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THE HISTOPATHOLOGY OF THE NERVOUS SYSTEM IN PELLAGRA *

H. DOUGLAS SINGER, M.D., M.R.C.P., AND LEWIS J. POLLOCK, M.D.
KANKAKEE, ILL.

The study of the nervous system in pellagra has been made, to a very large extent, only with the older methods of staining, and it is our purpose here to present the findings in a series of cases in which the more modern methods have been used.

The actual number of papers on the pathologic anatomy of the nervous system in pellagra is not very great and the conclusions reached are somewhat variable. By some the changes are regarded as characteristic and peculiar, whereas others see in the various findings only the expression of a generalized intoxication not in any way specific for this disease. The question is of some importance in relation to the widespread belief in the occurrence clinically, of a certain nervous and mental symptom-picture which is supposedly necessary for the diagnosis of pellagra. Another controversial feature, which stands out prominently, is the question concerning the relation of the vascular findings to the nervous changes and to pellagra itself.

The most recent[1] and extensive article on this topic is that of Kozowsky, whose results we shall have occasion to discuss in relation to our own findings. In this paper there is given a very extensive review of the literature beginning with the eighteenth century. As one might expect, Kozowsky comes to the conclusion that there is little of value prior to 1855, when there appeared a study of fourteen cases by Landouzy. Even at this time the brain was passed over as practically normal and attention was directed chiefly to the spinal cord in which were described softenings and sclerosis. As Kozowsky points out, the

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* From the Laboratory of the Illinois State Psychopathic Institute.

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1. Since this was written there have appeared two excellent papers, "Beitrag zur pathologischen Anatomie der Pellagrapsychosen" by A. Rezza. Ztschr. f. d. ges. Neurol. u. Psych., 1912, xii, 1; and "Des neurofibrilles dans la pellagre" by Millant. Arch. d. Neurol., 1912, xxxiv, No. 2, p. 312.

material is open to question, and but little stress can be laid on these findings. In 1881 Paussier called attention to the occurrence of fatty degeneration in the vessels and nerve cells of the brain and the presence of numerous amyloid bodies. He speaks of rare and restricted arteriosclerosis and reaches the conclusion that pellagra is a toxic disease similar to other diseases brought about by intoxications with food poisons.

From this time on there is a gradually increasing definition of widespread changes in the nervous system. In 1883 Tonnini, besides meningeal changes, described fatty degeneration of anterior and posterior cornual cells. Hieronimus, in 1885, spoke of small-celled infiltration of the brain and ependyma with widening of the perivascular and pericellular spaces, proliferation of the ependyma of the central canal and inflammatory foci in the gray substance of the cord in corresponding regions. Neusser noted clouding and thickening of the brain membranes with adhesions and also atrophy, sclerosis or softening of the spinal cord. Marchi called attention to insufficient staining as evidence of degeneration of the fibers in the posterior columns, anterior horns and the spinal roots.

In 1889 appeared an important work on the spinal cord by Belmondo based on twenty cases. He divided the changes into acute and chronic. The former were found in those cases ending clinically with the so-called typhoid-pellagra, and consisted in changes which belong to the pathological picture of an acute meningomyelitis. The chronic changes consisted in sclerosis of various tracts of the cord, which in the severe cases were supposedly constant and represented a systemic combined posterolateral sclerosis. Accompanying this, there was pigmentary degeneration with atrophy and loss of processes in the ganglion cells of the sympathetic and spinal systems. He also mentioned the frequent occurrence of chronic leptomeningitis with "arachnitis ossificans."

Tuczek, 1893, described systemic sclerosis of the posterolateral columns of the cord and contrasted them with the lesions in tabes dorsalis. He also mentioned especially the pigmentary degeneration of the spinal and sympathetic ganglia and described the occurrence of proliferation of the glia without, necessarily, any implication of the vessels. This is also the first article in which granule cells (probably identical with those known under this name to-day) are specifically noted. He also pointedly minimizes the importance of the previous findings of cerebral vascular hyperemia, anemia, pial edema and meningitis, as well as occlusion of the central canal of the cord.

P. Marie, 1894, discussed and supported Tuczek's findings in regard to the posterolateral sclerosis of the cord and its distinction from tabes.

Lombroso, in 1898, published an important monograph giving the results of 113 autopsies. He laid much stress on the occurrence of men-

ingitis, which in some cases was purulent; arachnitis ossificans; pigmentation or fatty degeneration of the adventitia of the vessels; pigmentation of the ganglion cells of the sympathetic and whole central nervous system; degeneration of pyramidal and posterior columns, with numerous "granule cells." He also mentions softening of the cord with phenomena of poliomyelitis and numerous corpora amylacea in the spinal cord and sympathetic system.

Babes and Sion, 1899, emphasized the pigmentation and chromatolysis of cells in the brain and the presence of pigment in pericellular and perivascular spaces, as well as a degeneration of fibers in the posterior roots, ascending cerebellar tract and Lissauer's zone. Similar findings in many respects have been made by other more recent authors and will be discussed in dealing with the changes of particular elements of the nervous system. All these papers deal, as will be seen, with the nervous lesions as a more or less primary condition. There must now be mentioned papers by Kozowsky, 1904; Mannini, 1905 and Alpago-Novallo, 1905, who laid particular emphasis on the presence of vascular lesions of arteriosclerotic character, which they claimed to be, to a large extent, the cause of the nervous lesions. This same view was reiterated and amplified by Kozowsky in a more extensive paper in 1912. Lukács and Fabinyi, in 1908, as the result of the study of three cases, minimized the vascular findings in their relation to the nerve lesions.

MATERIAL

The cases studied, fourteen in number, had all presented clinically, unquestionable evidences of pellagra. This was complicated in all but two by the presence of some form of mental disorder. They may be subdivided into two groups, the first of which comprises those patients dying during the acute or subsiding stages of the pellagrous attack. Of these there were eleven. (We have also examined the nerve cell changes only, in one other case.) Seven of them died at a short interval after the skin lesions had subsided, with clinical symptoms of "central neuritis." In the other five there were no symptoms, such as evidence of pyramidal tract lesion (Babinski reflex, jactatoid spasms, etc.) to suggest central neuritis, although diarrhea with rapid and progressive emaciation and weakness were almost always present. In only one of these twelve cases was there any complicating acute disease. This patient suffered from an attack of facial erysipelas three weeks before death, which ran the usual course with recovery, but had as sequelae an abscess due to breaking down of cervical lymph-nodes and double otitis media. Pus was still present in the neck at the time of death, but the abscess cavity was healing.

The second group includes three patients dying of intercurrent disease (lobar pneumonia, acute pulmonary and pleural tuberculosis, and chronic pulmonary tuberculosis, respectively) at certain periods after the

subsidence of all pellagrous manifestations; that is to say, after apparent recovery. In one the interval was three and one-half months, and in each of the other two, eighteen months. Certain significant differences were observed in the histology of the cases in the two groups, which will be described in detail below.

The age of the patients at death ranged from 35 to 71 years. Five were suffering from senile dementia, ages 66 to 71 (two of these belonged to the interval cases). Four were old-standing cases of dementia praecox, aged 36, 50, 51 and 51, respectively. Two were suffering from a manic-depressive type of psychosis, aged 35 and 36. Two were not insane, aged 43 and 57. The clinical history of both of these last is published in detail in the Report of the Illinois Pellagra Commission.[2]

TECHNIC

1. Tissue fixed in 10 per cent. formol and imbedded in paraffin: (1) Toluidin blue. (2) Thionin. (3) Cresyl violet. (4) Pappenheim-Unna. (5) Heidenhain's iron-hematoxylin. (6) Weigert's iron-hematoxylin and Van Gieson's stain. (7) Weigert's resorcin-fuchsin stain. (8) Osmic acid and toluidin blue for degeneration products.

2. Tissue fixed in 10 per cent. formol, after-mordanted in Weigert's glia fixing solution. Frozen sections: (1) Alzheimer's method No. IV for protoplasmic glia with Mallory's phosphomolybdic acid hematoxylin. (2) Alzheimer's method No. V. with Mann's stain.

3. Tissue fixed in 10 per cent. formol, after-mordanted, embedded in celloidin and stained according to Mallory's glia fiber stain.

4. Tissue fixed in 10 or 12 per cent. formol. Frozen sections: (1) Thionin, (2) Daddi-Herxheimer fat stain. (3) Smith's nilblue sulphate for differentiating fats. (4) Bielschowsky-Pollack silver impregnation.

5. Tissue fixed in alcohol. Celloidin-embedding. Thionin and toluidin blue.

6. Tissue fixed in 10 per cent. formol after-mordanted in Müller's fluid, embedded in celloidin: (1) Weigert-Kultschitsky-Wolters myelin-sheath stain. (2) Marchi method.

GROSS ANATOMY

The gross morbid anatomy of the nervous system was in no manner characteristic or pathognomonic. The skull presented no marked changes. At times there was thickening and at others thinning of the calvarium. The dura mater in the majority of cases was thickened, streaked with increased formation of connective tissue and in a few instances adherent to the pia mater. The pia-arachnoid was cloudy, opaque, edematous and thickened; at times lifted from the brain by the collection of fluid beneath it. The edema and thickening were most prominent over the convexity of the brain. In a few cases the pia-arachnoid was adherent to the underlying cortex. The spinal meninges showed similar changes to those noted in the cerebrum. Small bony plaques were occasionally observed. Neither *état criblé* nor punctate

2. Cases J. V. and A. D., Report of the Illinois Pellagra Commission (in press). Condensed Report, THE ARCHIVES INT. MED., 1912, x, 123, 219.

hemorrhages were met with in any case. The basal ganglia, cerebellum, pons and medulla were generally negative. In one case several hemorrhagic areas were observed in the mid-brain, but subsequent examination showed these to be, in all probability, artefacts.

MICROSCOPIC EXAMINATION

1. *The Pia Mater.*—Great stress has been laid on edema and chronic inflammation of the pia by the older authors.

The pia showed, constantly, changes of moderate severity consisting in thickening of the connective tissue with proliferation of fibroblasts. In a few cases the glia of the cortex was observed invading the thickened pia. This was especially true about the sulci. The more pronounced changes were in the vessels. The cells resulting from the proliferation of the vessel wall contributed largely to the formation of an exudate which was found in many cases. This exudate contained, besides the vessel cells, which were swollen and undergoing fatty degeneration, fatty and fibrinoid pigment granules and a few lymphocytes. Leukocytes were found in only one case, in which there had been an attack of erysipelas before death. Plasma cells were present in two cases, both complicated by pulmonary tuberculosis. No basophil cells were found in any case. The exudate was very small in amount in comparison with such diseases as cerebral syphilis, general paralysis, etc.

The thickening and vascular change was most marked over the convexity of the brain and was only severe in one case, in which it was universal, involving even the membranes lying within the folds of the cerebellum. Similar changes to those described above were also found in the pia of the spinal cord.

2. *Vessels.*—The changes found in the vessels may be described under two headings according as they are acute or chronic. The former may be directly related to the pellagra, whereas the latter certainly are not.

The chronic changes were most evident in the larger arterioles and consisted in thickening of all coats with some proliferation of vessel cells. These latter were also swollen and often contained various pigment granules. Some of the endothelial cells were shrunken and pyknotic and frequently contained various granules of degenerative material. Twisting, curling and the formation of ropes by the twisting of three or four vessels, together with splitting of the intima and curling of the elastica, were met with only in those cases showing senility or chronic alcoholism. About the vessels numerous granules of fatty and fibrinoid character were seen and in a few cases granules showing basophilic properties. Granule cells (*Abraümzellen*) containing fatty and fibrinoid material were especially frequent.

The smallest vessels also to some extent showed the more chronic thickening, with, in a few cases, splitting of the intima. All the changes described above seemed to be related to age or general intoxication with alcohol. In no case was there observed any hyaline change in the vessel wall and in none were there any suggestions of occlusion. In three cases small hemorrhages were found, two in the spinal cord (gray matter) and in one in the mid-brain. These hemorrhages were not surrounded by any reaction zone or degeneration, the extravasated blood-cells and nerve cells lying within the hemorrhagic area stained well, the latter showing well-preserved Nissl granules. It was, therefore, concluded that they were probably artefacts and produced *post mortem*. No other punctate hemorrhages were observed in any case.

The more acute changes were observed in connection with the smallest vessels. The intima was thickened by proliferation and the endothelial cells were at times swollen and at others shrunken and pyknotic. Fatty degeneration was common and in a few instances the intima was found to be split, but few if any cells were present in the spaces thus formed. The muscle cells were proliferated, swollen and distorted, being elongated or sac-like, poor in chromatin and contained pigment of various kinds. The adventitia was thickened with proliferating cells showing various kinds of degeneration. These changes in some cases were extremely slight.

In one case in the whole of one set of specimens, there were found in the adventitial cells a number of metachromatic basophil bodies which presented various shapes; rosettes, curved and elongated masses with small projecting buds or lobules, etc. These bodies resemble very closely those described by Borrel in carcinoma, and to some extent those of Councilman in variola. They possibly represent, as suggested by Professor Zeit of the Northwestern University, a form of mucoid degeneration. They evidently require some special conditions for their staining, for we were unable to demonstrate them again even with an apparently identical technic and in the same brain. They stained a purplish red with thionin, somewhat similar to the color of the nuclei in these particular specimens and might, if not degenerative products, be cell nuclei. Some of the specimens do, indeed, somewhat resemble mitotic figures, and this explanation seems the more probable.

In all cases there was more or less perivascular infiltration, consisting of vessel cells, pigmented and degenerating lymphocytes, fatty and fibrinoid pigment granules, glia cells and *Abraümzellen*. No basophil cells were observed in any case. Plasma cells were found in considerable numbers in one case, while in a second there were a few. Both of these patients had died of tuberculosis. Leukocytes were present in the exudate

in one case only, in which the patient had suffered an attack of erysipelas three weeks before death.

New vessel formation and "process cells" were found rarely in one or two cases. *Stäbchenzellen* occurred in numbers not exceeding the normal limits. Twisting of vessels and the formation of ropes similar to that described in the pia was present only in association with senility and chronic alcoholism. Widening of the perivascular spaces was also observed under the same conditions. The lumen of the minute vessels in the gray matter of the spinal cord was usually somewhat widened, and it was in this same position that the minute hemorrhages described above, probably artificially produced, had occurred.

No example of *état criblé* or blood-cyst was observed.

The exudate here described was of moderate degree in all cases and in some had to be sought with a high power in order to demonstrate its presence. It was not, in any degree, to be compared with the exudates which form such a striking picture, even with a low magnification, in specimens from general paralysis, lues cerebri, trypanosomiasis, etc. Although it probably has a relation to pellagra as an intoxication, it was also present in very similar degree and constitution in those patients dying at some considerable interval after the subsidence of all clinical evidence of pellagra, and in these can probably be related to the acute toxic and infective diseases which caused death. There is nothing in the picture to suggest a local invasion of the nerve tissue with micro-organisms.

As already indicated, much stress has been laid on the changes in the blood-vessels in pellagra by several authors, notably Kozowsky, Mannini and Alpago-Novallo. Kozowsky, especially, alleges that vascular lesions are the cause of many of the changes in the nerve tissue. This is particularly inexplicable for the reason that he selected his material with extreme care and laid down the following conditions before admitting it for use in studying the pathology of pellagra. He insisted on: (1) the presence of characteristic symptoms in each of the skin, gastro-intestinal, nervous and psychic systems: (2) the absence of previous alcoholism, syphilis and bad surroundings; (3) the patients must be under 40 to 45 years of age. Yet in spite of these conditions, which he claims to have filled in all of his cases, he found frequently hyaline degeneration of the vessels at least in some organs of the body, with small focal softenings, old blood cysts, punctate hemorrhages and an *état criblé* in the brain. It might also be added that in most cases he found an advanced degree of sclerosis of the liver and spleen and describes the former organ as grating under the knife on section (*"Knirscht unter dem Messer," "lässt sich nur schwer schneiden"*). In view of our findings with cases considerably older and in some suffering from the effects of chronic alcoholism, one

cannot but feel that there must have been some other factor at work. The importance of the vascular changes in relation to pellagra have also been minimized by Tuczek and more recently Lukács and Fabinyi.

3. *Neuroglia.* — (a) *Fibers.* In all cases there was more or less increase of glia fibers in the outermost layer of the brain cortex, which was especially marked in and about the sulci and around the vessels. In the network thus formed there were numerous amyloid bodies (Plate I, Fig. 26). In some cases the glia fibers were found invading the pia, causing adhesions between it and the brain. Similar increase of glia fibers was also present in the spinal cord, especially around the periphery and about the central canal. The increase of fibers was in no case as marked as is usually found in senile dementia.

(b) *Cells.*—Although there were found several types of glia nuclei and cell bodies with thionin staining, no definite conclusions can be drawn from them, inasmuch as the normal limits of glia cells in this respect are poorly defined. In the superficial layers of the cortex were observed a large number of pyknotic distorted cells with long fibers, the nuclei being star-shaped, lanceolate, biscuit-shaped, semilunar, etc. The protoplasm stained but poorly. Many pigment granules were present within these cells, staining bluish-red or pink with thionin. In the deeper layers of the cortex were found glia cells with a small, dark nucleus rich in chromatin and a small amount of faintly staining protoplasm. Also cells with a swollen, pale nucleus containing but a few fine chromatin granules and perhaps one or two pink nucleolus-like bodies. The nuclei frequently fill almost the entire cell body, and show many types of distortion into various bizarre shapes. A cell with a large nucleus of the same character and more deeply stained protoplasm was likewise seen. In the white matter there were two chief types of cell, one with a small dark and the other with a large pale nucleus.

Fatty degeneration of the bodies of the glia cells in the cortex was constant in marked degree. The bodies of these cells likewise contained other pigment material staining blue, green and reddish with thionin. In two cases, one of chronic alcoholism and the other with septic infection following erysipelas, a few giant glia cells containing two or more nuclei were found.

Satellitosis was constantly present in varying degree, depending on the amount of chronic change in the ganglion cells. At times a number of satellites were found directly about a ganglion cell, sometimes forming a fence about it with a space between them and the ganglion cell. The satellite cells were especially numerous about the cells undergoing degeneration and the shadow cells. They were not present in increased number about the cells showing axonal reaction.

The *astrocytes* (Plate I, Figs. 19-22) in all cases were definitely increased in number, especially in the deeper layers of the cortex and in the white matter, but not to the degree met with in general paralysis nor so marked as is usually found in senile dementia. The two most marked examples were cases of senility and chronic alcoholism.

These cells stained with Alzheimer's Methods IV and V, showed various interesting conditions. The cell processes were usually thickened and presented darkly-staining streaks of wavy outline. They frequently appeared to be broken. Occasionally the processes were small and thin.

The bodies of these cells were either large or comparatively small. Where large they were more homogeneous. Granular transformation of the protoplasm was frequently observed. The granules corresponded to the Alzheimer methyl blue granules, and probably indicate a degenerative condition. The nuclei showed various shapes and contained granules. They were cresentic, elongated, round or oval, central or displaced to the periphery of the cell. At times very little of the cell body was visible around a large, distorted nucleus from the vicinity of which issued darkly staining fibers. Occasionally a peculiar staining reaction was noticed in the cell bodies apart from the granularity.

The relation of the astrocytes to the vessels was variable. Some were found at a short distance from, but parallel to, the vessels, others encircled them, and still others existed apparently quite apart from the vessels in the surrounding tissues. Those in direct relation with the vessels were attached to the walls by insertion feet of various shapes and sizes. In many instances they were bent and twisted. In nine of the thirteen cases these insertion processes were definitely thickened (Plate I, Figs. 19, 22), whereas in one they seemed definitely smaller than usual. This was an interval case, aged 71, the patient dying from acute pleural and pulmonary tuberculosis.

In seven cases a cystic degeneration (Plate I, Fig. 19) of non-fatty character was found, similar to that described by Cerletti in cases of pernicious malaria, but also observed in other conditions. This cell picture should be differentiated from the cyst-like change associated with fatty degeneration. The cell protoplasm has disappeared in part or whole, to be replaced by numerous small or large, pale and apparently empty vesicles. These are present around the nucleus, and at times at some distance from it, or along some thickened process. From between the vesicles many processes, usually thin, can be seen to issue. The significance of this change is unknown, but its appearance suggests a degenerative condition. In all but one of the seven cases showing this type of cell, the patients had been either senile or the subject of chronic alcoholism. All three of the interval cases presented these cells and died with infective disease.

Giant astrocytes were found in five of the thirteen cases studied with the special glia stains. Two of them in younger individuals with manic depressive insanity and dementia praecox dying from pellagra, two with chronic alcoholism and one, an interval case, dying from chronic tuberculosis eighteen months after the disappearance of all symptoms of pellagra.

The increased number of astrocytes is not as marked as is usually found in senile dementia, but we cannot agree with Kozowski when he states that an increase of astrocytes is the exception rather than the rule.

The significance of an increase in astrocytes such as is here described is still undetermined. According to Alzheimer, Weber and Schroeder, it would indicate the presence of an active disease process, whereas Orlow and others find them more numerous in chronic conditions. The cases here studied can throw no light on this question, as both chronic and acute changes are present.

A variety of glia cell to which Alzheimer has particularly called attention and to which he ascribes much importance is the *ameboid transformation* of astrocytes and small glia cells. The ameboid glia cells (Plate I, Figs. 23-24) have been found by Alzheimer particularly in recent and active diseases of the brain. Never in old hemorrhages, old-standing softenings, old cases of dementia praecox, in epilepsy after a long period free from convulsions nor in manic depressive insanity. On the other hand, they are present in severe infection deliria, alcoholic delirium, acute stages of dementia praecox, many cases of status epilepticus, many cases of general paralysis and lues cerebri, acute and subacute experimental intoxications, uremia, diabetic coma, sepsis, etc. Ameboid glia cells are seen most frequently in the deeper layers of the cortex and in the white matter. They present several forms: (1) A small body with few pseudopodia and comparatively large nucleus, they are found chiefly about the vessels; (2) a cell with a large homogeneous body and numerous large pseudopodia. Frequently these cells are seen to surround a degenerating axone. Many surround a vessel matting together around it. Within their bodies are found pigment granules of various types. Granular change was frequent. Fatty degeneration was observed in one case which had suffered from erysipelas. Fat pigment was frequent. Ameboid cells were found in all cases in one or another form. It should be added that the interval cases all had some toxic or infective process to explain their presence.

Many astrocytes were seen undergoing the transformation into ameboid cells, sometimes while still clinging to a vessel by means of the insertion process (Plate I, Fig. 21). Occasionally there were found ameboid cells, the bodies of which had coalesced and hence contained two or more nuclei. Along the vessels were found a number of examples

of this type of cell. Besides these, a number of small cells with round nuclei and a small amount of granular protoplasm were found lying along the vessels or scattered through the white matter. Processes were never seen issuing directly from these cells, but many thin processes radiated about them, and when examined in mass appeared to belong to the cells.

At this point attention may be directed to the condition of the *central canal of the cord* (Plate I, Fig. 27), which was found to be occluded and changed in all but one of the cases. Such a condition is probably not abnormal in any adult (Schmaus, Ziehen, et al.), but it should be noted that here there seemed to be a definite central gliosis, and not merely a collection of débris and degenerated epithelial cells.

The processes of the ependymal cells interlaced with the fibers of the numerous glia cells to form a network in which were embedded amyloid bodies in varying number. The ependymal cells were rich in chromatin and when altered were usually swollen. Many layers of such cells were present, all semblance of the normal arrangement being lost. Small round nests of these cells were often observed scattered through the area occupied by the gliosis.

4. *Nerve Cells.*—The *cyto-architecture of the cortex* was only slightly disturbed. The changes were most marked in the layers of large pyramidal cells. They consisted in paucity of cells with a change in their relative positions and increase of glia elements. In no case was there a disturbance as severe or marked as that seen in general paralysis.

The changes in the ganglion cells of the nervous system were extremely marked and of great importance. They may be divided for consideration into two groups: (1) The indirect or axonal types of reaction, (2) the direct reaction types.

1. *Indirect or Axonal Reactions.*—Two grades of intensity of this type may be recognized.

(a) *Typical Axonal Reaction* (Plate I, Figs. 1-4, 9, 10, 18).—In this condition, which can be produced experimentally by injuries to the axone (Marinesco, van Gehuchten), the cell is swollen and rounded, the nucleus is displaced to the periphery where it may form an actual projection on the surface, or may even be extruded altogether. The tigroid substance has for the most part disappeared from the central portion of the cell, blocks, staining well, being often left around the periphery and especially in the base of the larger dendrites and a considerable mass around the nucleus. The nucleus is distorted, often oval or reniform, stains more or less uniformly with a pale color and there is a well-preserved nucleolus rich in chromatin.

(b) *Central Chromatolysis.*—Cells presenting a body which is not swollen has a central well-preserved nucleus and darkly staining nucle-

olus. The Nissl granules have largely disappeared from the central portion of the cell, but large blocks are present about the periphery and often also immediately about the nucleus. It differs from the last in the absence of swelling and displacement of the nucleus.

There was a marked difference between the cases examined at some interval after the pellagra attack and those in which death occurred during, or soon after, an acute outbreak. Of the *interval cases,* two died eighteen months, and one three and one-half months after the attack. The two former showed practically no axonal change at all; in the last it was present to a much less degree than in the acute cases. In one of the older cases no axonal change was found in the brain or cord even in the Betz cells or in the cells of Clarke's column, and only one anterior horn cell, situated in the dorsal region of the cord, presenting this change, was found. In the second many of the Betz cells were entirely healthy, although a few showed central chromatolysis without nuclear displacement. In the cord a few cells in Clarke's column showed typical axonal change as did also some of the cells of the semilunar ganglia of the sympathetic. In the case dying three and one-half months after the subsidence of the pellagrous attack a moderate number of the Betz and large pyramidal cells in the anterior central and paracentral convolutions showed axonal change, while most presented a picture of central chromatolysis without displacement of the nucleus. In this case also some cells showed a granulation with homogeneous, non-metachromatic, basophil particles not found in any other case. This change has been described in acute infective diseases and is possibly related to the tuberculosis, which was the cause of death.

In the *recent cases* axonal changes were severe in all, and in many involved practically all the Betz cells and many of the large pyramidal cells of the central convolutions. Similar changes were also found in the ganglion cells of the hippocampus, the dentate nucleus of the cerebellum, the central ganglia, and the nuclei of the cranial nerves.

In the cord these changes in the cells of Clarke's column were constant and often extreme; they were present in more or less of the anterior cornual cells in eight of twelve cases, in the posterior cornua in four (in one of these more marked than in the anterior cornua). Similar reactions were found also in the posterior root ganglia and in the cells of the semilunar ganglia of the sympathetic and of Auerbach's and Meissner's plexus in the intestine in the cases in which these were examined.

It is noteworthy that on the whole the Purkinje cells of the cerebellum were the best preserved cells of the whole brain. Some showed central chromatolysis, but none true axonal change.

The cell showing axonal reaction is, except in very severe degrees, capable of recovery and the above facts would suggest that the change is

the result of the condition, whatever it be, which underlies the acute pellagrous outbreak. During the interval the cells again resume, to a greater or less extent, their normal state. This type of reaction also seems to result from an injury to the neurone at a distance from the cell and such an hypothesis is well borne out by the absence of satellitosis about these cells noted above.

This one feature thus seems to bear the most definite relation to the acute pellagra attack. With it is probably to be related the scattered Marchi degeneration found throughout the nervous system. This particular picture of widespread axonal chromatolysis with special involvement of the Betz cells and those of Clarke's column has been noted by all workers on pellagra with modern methods of staining (Marinesco, Babes, Lugaro, Anderson and Spiller, Kozowski and others). As has already been noted by one of us, the picture is identical with that described by Meyer under the title of central neuritis. In a personal communication, this author assures us that none of his cases presented clinically a picture of pellagra. Attention may also be drawn, in this connection, to the publications on this syndrome and on the cytology of the brain in mental disorders by Cotton and Southard, Coriat, Somers, Orr and Coles. In a case of chronic alcoholism recently studied by us, there was, clinically and pathologically, a picture of central neuritis, and yet nothing to suggest a history of pellagra. Indeed, it would be impossible to distinguish microscopically between the specimens of this case and those here described. We must, therefore, conclude that pellagra is not capable of recognition *post mortem* (apart from the presence of the typical skin lesions). This is contrary to the opinion expressed by Kozowski in his very detailed report of cases with an excellent digest of the literature. It is of interest here to call attention to an oft-quoted case published by Righetti in which he specifically speaks of "polyneuritis" in a case of pellagra. This, as far as we have been able to find, is the only reference to the occurrence of neuritis in pellagra. The examination concerned only the spinal cord and peripheral nerves, and, while the axonal changes in the gray matter and sympathetic system were entirely similar to those described above, there was also a focal hematomyelia in the lumbar region with clinical symptoms suggestive of such a lesion. It is even more striking to find that, as specifically stated, there was no clinical history of pellagra, and the diagnosis was made chiefly on the grounds that the patient's mother had had pellagra, and she was living under conditions which favor its occurrence. Such a conclusion might be correct, but is not justified by the facts.

The interpretation of these changes is possible in only one way, namely, that such a picture as that presented in central neuritis is a mode of reaction to some harmful agent circulating in the blood, acting

on the axis-cylinder processes of the neurons at some point in their course. Further, it seems clear that this change may be brought about by various ultimate causes, although it is conceivable that the actual excitant of the reaction is the same in all and a product of body metabolism under morbid conditions.

2. *Direct Cell Reaction.*—The result of immediate injury to the cell.

Under this heading no distinctions can be drawn between the interval and recent cases. The various types of cell met with may be grouped under the following headings:

Type 1.—Cell body shrunken and distorted with crenated edges but in some cases normal in size, more or less uniformly staining, pale in color. Nucleus rich in chromatin.

Type 2.—Similar cell bodies with pale nucleus which may be of the same color or lighter than that of the cell body which may be reticulated. Within the nucleus or nucleolus are granules staining a bluish green with thionin. In some of these the nucleus is lost, with or without the nucleolus.

Type 3.—Shrunken, uniformly dark-staining cell body and dark nucleus sometimes filling almost the whole cell.

Type 4.—Simple chromatolysis. Body normal or a little larger. Nissl granules are scattered diffusely throughout, rarefied and pale or present only as a fine dust. Nucleus approximately normal in staining and position. Nucleolus dark.

Type 5.—Shadow cells, a more extreme degree of the same type as the last. Nucleus absent. The outline of the cell indistinct.

Type 6.—Vacuolated cells. Nucleus present. No Nissl bodies. The cell body contains vacuoles.

All the above types of cell change, with the exception of Types 5 and 6, are found in all regions of the cortex in all cases, although generally most marked in the central and paracentral convolutions. Either shadow or vacuolated cells were present in all but four of fourteen cases. Similar changes belonging more especially to Type 3 were also found in the cells of the gray matter in the cord, most noticeably in the posterior cornua.

In association with these direct types of cell reaction there was more or less well-marked satellitosis. Such cell changes, first described by Nissl, have been the subject of numerous investigations (Marinesco, van Gehuchten). Marinesco, in particular, contrasts them with those we have described under the head of indirect or axonal reactions and considers that they are the result of direct injury to the cells themselves. Some of the types belong to the picture of acute change and have been produced experimentally by the administration of various intoxicants, such as lead, arsenic, etc., and are also observed in the acute infectious diseases; others are more chronic and represent the result of subacute or chronic poisoning. A further indication that these changes are the result of intoxication of the cells directly by noxious agents is also shown by the presence of satellitosis, which, as we have mentioned, is absent around the cell showing the indirect or axonal type of reaction. The other glial

reactions found in the cortex and white matter must also be regarded as indications of active acute and chronic disease processes, showing both progressive and regressive types of changes.

The relation of these changes to pellagra is extremely difficult to determine. The fact that they are present in the interval cases cannot be considered as excluding a dependence on the pellagrous disorder, for similar changes can unquestionably be brought about by various toxic agents and must be regarded as merely a type of reaction to damage. All the interval cases were suffering from infections which might well cause a similar reaction to that of pellagra. Attention should also be called to the fact that two of our patients were suffering from pellagra without complicating psychosis or infectious disorder and hence one would be inclined to attribute the direct cell reactions and glial changes found in them to pellagra. In order definitely to settle the question of the presence of chronic cell change with satellitosis as a part of the pellagrous disease during the period when there are no clinical symptoms observable, it would be necessary to study uncomplicated (especially by chronic mental disorders) interval cases in which the patients died at a sufficient length of time after the acute attack to permit the disappearance of the nerve lesions which result from such acute exacerbation. This unfortunately, we have so far, been unable to do. The question is an important one, for if such changes do persist, there would be ample basis for the occurrence of a more chronic dementing pellagrous insanity, the existence of which must be still considered as *sub judice*.

Fibril Changes (Plate I, Figs. 11-18).—The neurofibrils were successfully stained in ten of our cases and showed similar changes in all, including the interval cases. The changes found consisted in:

1. Agglutination.
2. Fragmentation.
3. Loss of fibrils (in small cells only, with one exception referred to below).
4. A peculiar encircling of the nucleus and pigment masses with agglutinated fibrils, not, as far as we are aware, previously described in pellagra.

In only one case (senile dementia of severe grade) were the fibrils found to be absent in large cells. In this case the fibrils, when present, showed the reticular formation usual in senile dementia. This case also showed advanced chronic Nissl changes in the cells, with reticulated protoplasm and extreme fatty pigmentation.

The reports of fibril changes in pellagra are somewhat scanty. Parhon and Papinian report one case in which they found complete loss of fibrils in the large pyramidal and Betz cells. This, as already pointed out, is certainly the exception. The neurofibrils have been the subject of exten-

LEGENDS FOR PLATE

Figs. 1-4.—Cells showing axonal type of reaction. 1 and 2 from the cerebral cortex; 3, from the spinal anterior cornu; 4, from a sympathetic ganglion. (Nissl staining.)

Figs. 5-6.—Pyramidal cells from the cerebral cortex showing fatty degeneration. (Nissl staining.)

Figs. 7-8.—Pyramidal cells from the cerebral cortex showing basophilic degeneration. (Thionin.)

Fig. 9.—Cortical pyramidal cell showing axonal change and fatty degeneration. (Osmic acid and toluidin blue.)

Fig. 10.—Fatty degeneration and axonal change in a cortical pyramidal cell. (Scharlach and hematoxylin.)

Figs. 11-18.—Fibrillary changes. (Bielschowsky.) In 14 note the double ring formation. Figure 18 represents the neurofibril picture in a cell showing axonal change.

Fig. 19.—Astrocyte (Spider cell) undergoing cystic degeneration. Note the thick insertion foot. (Alzheimer IV.)

Fig. 20.—Astrocyte showing twisted insertion process. (Alzheimer IV.)

Fig. 21.—Astrocyte undergoing ameboid transformation. (Alzheimer IV.)

Fig. 22.—Astrocyte with thickened insertion process. (Alzheimer IV.)

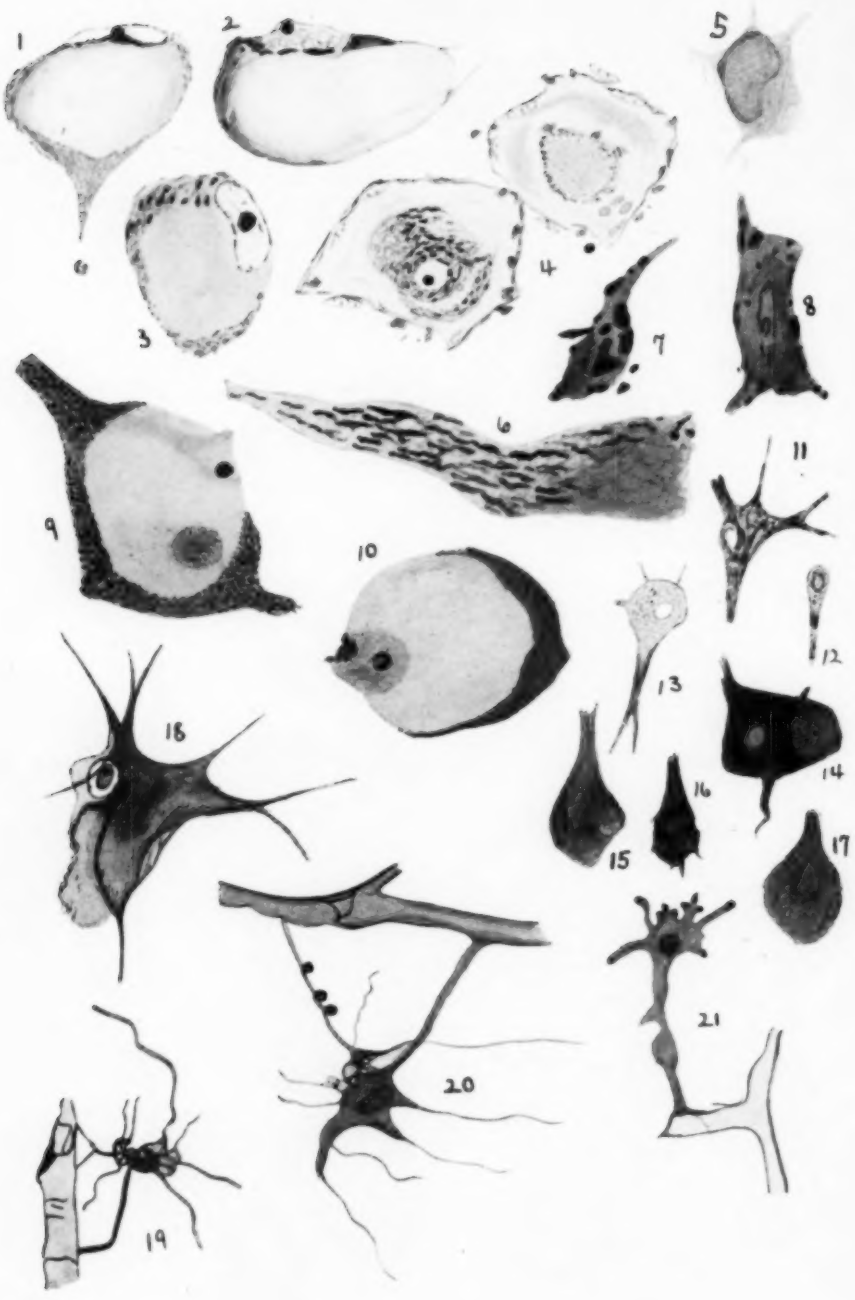
Fig. 23.—Ameboid glia cell. (Alzheimer IV.)

Figs. 24-25.—Ameboid glia cells with coarse granulations. (Alzheimer IV.)

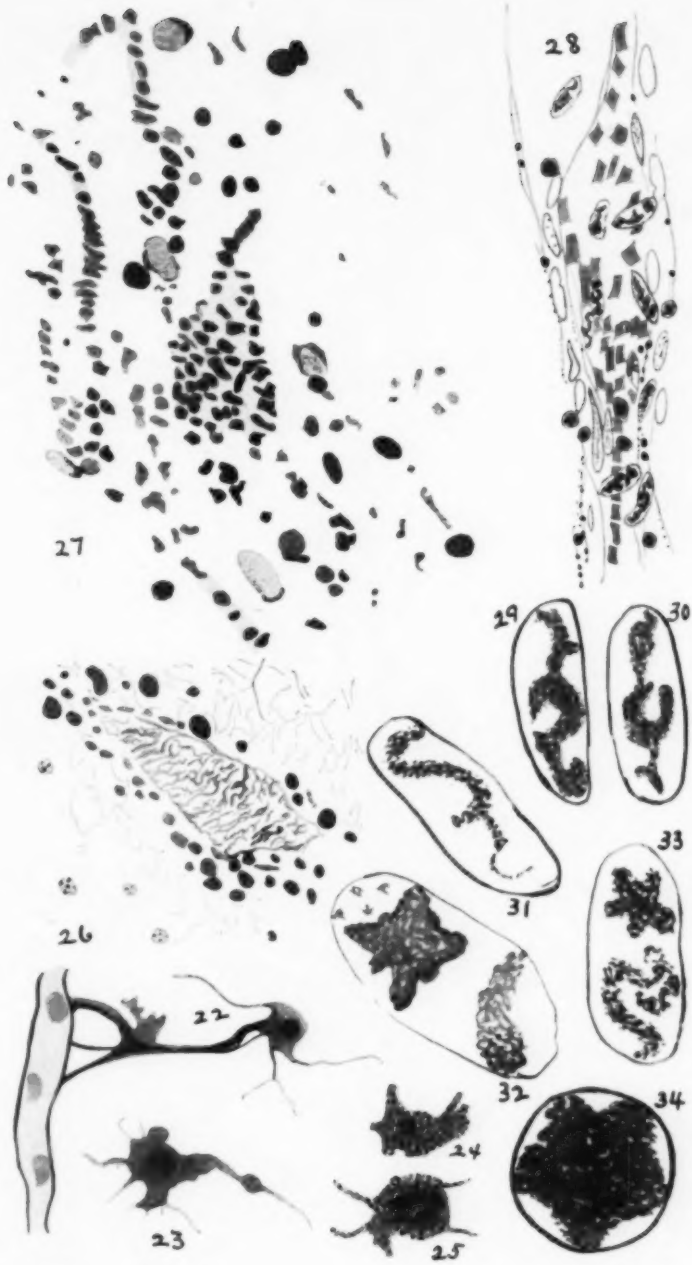
Fig. 26.—Amyloid bodies about a vessel. (Unna-Pappenheim.)

Fig. 27.—Central canal of cord showing distortion and gliosis.

Figs. 28-34.—Inclusion forms in muscle and adventitial cells of small vessels from Case 1. Figure 28 shows the number of these bodies under a low power. Note the apparent mitotic figures in Figures 32 and 33. Figure 34 is a transverse section. (Thionin.)



Illustrating Article by Drs. Singer and Pollock
The Archives of Internal Medicine, June 15, 1913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sive study in recent times (Bielschowsky, Simchowicz, Alzheimer, Fuller and many others), and there is a strong tendency to regard them as of extreme importance in the nervous functions of the neuron. If this is correct it seems probable that a complete loss of fibrils must mean a complete loss of function and most likely an impossibility of recovery of the neuron in question. The clinical study of pellagra would make the presence of this sequence of events in this disease at least highly improbable.

It is interesting to note that, in spite of the advanced age of some of the patients studied by us, no Redlich-Fischer plaques were found and none of the Alzheimer basket-cells were encountered. Three other cases besides the one mentioned above showed senile reticular fibril distribution.

In all cases there was noted a marked paucity of processes in the larger cells which was especially striking in the specimens impregnated with silver.

Pigmentary Degeneration (Plate I, Figs. 9, 10). — Pigmentary changes were marked in all cases, including even those of younger age. This pigment was present in all types of cell change, as well as in cells showing normal staining and formed a very prominent feature in the Betz, large pyramidal and other cells showing axonal change. The pigment stained black with osmic acid, red with scharlach and blue with nilblue sulphate. It formed large masses at the base of the cell, sometimes extending around the displaced nucleus and into the protoplasmic processes. In many of the cells, basophil and fibrinoid granules were present in the nucleus.

Pigmentary deposits of fatty character of some degree may be considered as a normal phenomenon and the amount unquestionably increases with advancing age (Marinesco and others). Nevertheless, they have been found in a child of only two years (Pilcz). They are, in general, considered to be the result of a failure to remove all products of metabolism, whether this be due to faulty elimination or excessive production. Some have regarded them as the result of degeneration of the chromatin material of the cell (Babes). There can be no question that in the cases studied here they are of pathological extent, far exceeding the amount in which present even at an advanced age. This change in the nerve cells of pellagrins has been emphasized by many authors, notably Kozowsky.

5. *Nerve Fibers.*—With the *Marchi stain* the brains showed diffuse scattered degeneration of radial fibers in the cortex, but none was found in the supraradiary or tangential fibers. Nowhere did they form definite bundles.

In the spinal cord a few scattered, degenerated fibers were present in all regions, not in any way systemic, involving perhaps to the greatest extent the posterior columns, and especially the subpial fibers in two cases. The crossed pyramidal tracts did not seem to be more affected than the other regions and in some cases were practically free.

The anterior and posterior roots showed a few degenerated fibers, sometimes more marked in the cervical, sometimes in the lumbar region. In two cases the number of blackened fibers was quite marked.

It is somewhat striking that the pyramidal tracts show so little Marchi degeneration in view of the extremely widespread axonal change in the Betz cells of the cortex. This is especially important because the axonal changes are considered, as described above, to be the consequence of damage to the axone. Under this hypothesis one can only assume that the damage has not been sufficiently intense in most neurons, to cause degeneration of the nerve fiber, while yet enough to produce tigrolysis. On the other hand, it would perhaps be well to bear in mind that similar changes in the cell may conceivably arise in other ways, as, for instance, has been demonstrated by Warrington, in anterior cornual cells, as the result of section of the dorsal roots. In the cases here studied the former explanation has been considered the more probable, especially in the light of the recovery of the Betz cells seen in the interval cases.

Wolters-Kultschitzky Method.—In the cortex we attach no significance to the fact that, in some cases, there was poor staining of the tangential and supraradial fibers for the reason that, in such cases, the amount of staining appeared to depend entirely on the degree of differentiation. The need for care in interpreting such findings has been emphasized by Binswanger, Nissl, Alzheimer and others. Apart from this no definite changes were found in the brain. One case showed a cerebellar atrophy with defect in staining which can have no relation to pellagra.

In the cord all cases showed some loss of staining in Goll's column which was situated in most instances in the center of the column bordering the middle line. In a few it extended forward to the commissure, and in some involved fibers scattered throughout the whole column. Under a high power the degeneration was seen to affect quite scattered fibers, the majority being well stained, and from its situation it would appear to involve the endogenous fibers belonging to the septo-marginal area and those of the cornu-commissural zone rather than the main ascending tract.

In most cases this change in Goll's column was most marked in the cervical and might be entirely absent in the lumbar and lower dorsal region. In one case it was more marked in the dorsal than the cervical region. In two it extended up to the medulla. In two cases similar pale

staining was found in the crossed pyramidal tracts, in three in Lissauer's tract, in one in the lateral basis bundle, and in two in the lateral limiting layer of Flechsig.

The fiber degenerations in pellagra have been studied by numerous authors, notably Tuczek, Marie and Lombroso. The older authors claimed to find definite systemic degeneration, generally a combined postero-lateral sclerosis. Later work, however (Spiller and Anderson, et al.), seems to show clearly that systemic degenerations are certainly exceptional, and, as will be seen in the cases we have studied, they are not present.

6. *Amyloid Bodies and Pigment Granules.*—An excess of amyloid bodies is present in all cases and has attracted the attention of many writers. In many of our specimens they are present in very large numbers, both in the brain and in the spinal cord. They occur beneath the ependyma, along the vessels, in the thickened glia of the most superficial layers of the cortex and periphery of the spinal cord and also around the central canal. The origin of these bodies has been much discussed. According to the older views they represent degenerated axis cylinders or myelin sheaths (Siegert, Wolf and others) or glia cells (Obersteiner, Redlich and others). Obersteiner suggests that they are degenerative products occurring within the glia cell body which are at first surrounded by a layer of fat, and that when the cell undergoes disintegration these bodies are set free and the fatty envelope is dissolved. Recently, Alzheimer has suggested that they do not exist in the solid form during life, but are the result of precipitation of certain material from the tissue juices by the fixing fluids. Their meaning is not by any means clear, but they occur especially in chronic degenerative conditions such as the senium, etc.

The pigmentary degenerations of nerve cells have already been discussed and it is only necessary here to mention the presence of free pigment granules of fatty and fibrinoid nature in the tissues and perivascular lymph-spaces in all cases. In five of our cases there were also present granules taking a basic stain. These various granules, specially studied by Alzheimer, are found in all chronic degenerative conditions.

SUMMARY

There is present in the acute attack of pellagra and in the interval cases a picture compounded of acute and chronic types of reaction. The acute changes include direct and indirect chromatolysis of nerve cells, satellitosis, astrocytosis and the presence of ameboid glia cells. Under this heading would also come a very moderate amount of perivascular infiltration which indicates general intoxication.

The perivascular infiltration of the acute attack is not more marked than that found in the interval cases. This might be used as a further argument against an acute local infection of the nervous system during the acute outbreak of the disease.

The chronic changes include fatty and fibrinoid degenerations, chronic Nissl changes of the nerve cells, increase of glia fibers, regressive changes of the glia cells, permanent destruction of nerve fibers and a marked increase of amyloid bodies. Chronic vascular changes were found only in cases of chronic alcoholism and senility.

In addition to these changes, especial emphasis should be laid on the constant presence in all cases examined where death had ensued during or soon after an acute attack of pellagra, of the reaction known as central neuritis. Furthermore, this type of change was found to have almost entirely disappeared in two patients dying eighteen months after an attack, while still definitely present, though in mild degree, in a third patient dying three and one-half months after such an attack.

It would therefore appear that the acute attack of pellagra is often, if not always, accompanied by some general intoxication of special kind which disappears in some, if not all, cases in which recovery occurs. It must not be forgotten, however, that a similar reaction is found in diseases other than pellagra.

CONCLUSIONS

1. The acute pellagra attack is accompanied by evidence of both acute and more chronic intoxication.

2. In common with other intoxicative conditions, the acute pellagra attack gives rise to a "central neuritis" reaction.

3. None of the changes are characteristic of this particular form of intoxication.

4. There is no evidence of a local infection of the nervous system with micro-organisms.

5. From our cases it is impossible to determine whether the more chronic changes found in the absence of a recent pellagrous exacerbation belong to the pellagra picture.

6. There is no evidence to show that chronic vascular changes are essential to the picture of pellagra.

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BLOOD-PRESSURE VARIATIONS AS INFLUENCED BY RAPID CHANGES IN ALTITUDE. A STUDY OF 100 NORMAL MEN *

F. E. CLOUGH, M.D.
LEAD, SOUTH DAKOTA

In view of the fact that doctors practicing at moderately high altitudes are being told repeatedly by their patients that they must leave the country on account of their health and the influence the altitude has on their condition, a series of readings was taken to see if a change of from 1,400 to 1,700 feet would be of any importance on the blood-pressure.

The Homestake Mining Company, through whose courtesy this work was carried on, is a gold mining concern whose underground workings are naturally ventilated. This is accomplished by having shafts in different gulches, widely separated from each other, the current of air in some of them being downward, in others upward. The mine is quite free from gases because the character of the rock does not generate any *per se*. A small amount of carbon dioxid is present, due to the decomposition of dynamite, the burning of candles and acetylene lamps, and the exhalations of the miners. At the surface the humidity is very slight, while in the mine the air is practically saturated.

The elevation of Lead, South Dakota (pronounced Leed) is 5,250 feet above sea level. The shaft is 1,700 feet deep, having an altitude at its bottom of 3,550 feet.

The following table shows the barometric pressure at the different locations cited in this article:

Place	Altitude Above the Sea Feet	Approximate Mean Barometric Pressure	
		Inches	Millimeters
Sea level	0	30.	760
Lead, So. Dakota.....	5250	24.55	622
1700-foot level	3550	26.20	663

There is thus a difference of 1.65 inches barometric pressure between the top and the bottom of the mine.

The readings were taken on the miners of this company as they were preparing to go down the shaft to work and again as soon as the bottom was reached. Again, the readings were taken at the bottom after a day's work and then at the top as soon as the ascent had been made. To make the descent the men stood on a cage or elevator and went down 1,700 feet in approximately two minutes. Coming up, the journey was more rapid, only one minute being necessary. No attempt was made to pick out

* Submitted for publication March 27, 1913.

special men, for they were taken just as they came. They were of all ages and conditions and represent eight nationalities — Americans, English, French, Austrians, Finns, Germans, Italians and Scandinavians. No attempt was made to find out the history of previous diseases. These men were so healthy that they were able to carry on manual labor for eight hours each day, and none seemed to be worn out after the day's work.

All readings were taken in the standing position, the only practical way under the circumstances. The instrument used was a standard mercury sphygmomanometer with a 5-inch cuff placed above the elbow.

As stated above, the altitude at the top is 5,250 feet, at the bottom 3,550 feet.

The 100 men were divided as to ages as follows:

20 to 30	51
31 to 40	31
41 to 50	13
51 to 60	5

The average age is 32.42 years.

The following readings were taken (systolic):

Descending		Ascending	
Average at surface....	146.45 mm.	Average at bottom....	145.27 mm.
Average at bottom....	141.07 mm.	Average at surface....	139.94 mm.

The average pressure, according to decades, was a follows:

20 to 30 years. 51 men

Descending		Ascending	
Average at surface....	145.33 mm.	Average at bottom....	144.19 mm.
Average at bottom....	139.31 mm.	Average at surface....	138.43 mm.

31 to 40 years. 31 men

Descending		Ascending	
Average at surface....	144.28 mm.	Average at bottom....	141.25 mm.
Average at bottom....	138.96 mm.	Average at surface....	137.35 mm.

41 to 50 years. 13 men

Descending		Ascending	
Average at surface....	150.30 mm.	Average at bottom....	156.61 mm.
Average at bottom....	150.77 mm.	Average at surface....	159.23 mm.

51 to 60 years. 5 men

Descending		Ascending	
Average at surface....	157.60 mm.	Average at bottom....	152. mm.
Average at bottom....	146.40 mm.	Average at surface....	147.60 mm.

MAXIMUM PRESSURE BY DECADES

	Descending		Ascending	
	Top	Bottom	Bottom	Top
20 to 30 years	198	204	186	194
31 to 40 years	210	202	190	172
41 to 50 years*	222	226	208	208
51 to 60 years	210	184	170	166

MINIMUM PRESSURE BY DECADES

	Descending		Ascending	
	Top	Bottom	Bottom	Top
20 to 30 years	112	105	116	116
31 to 40 years	126	116	110	102
41 to 50 years*	222	226	208	208
51 to 60 years	136	120	116	110

*Immediately after this reading this man developed marked signs of pulmonary tuberculosis and is now unable to work on that account.

THE GREATEST VARIATION

Descending				Ascending			
Age	Top		Bottom	Age	Bottom		Top
35	121	to	142	40	120	to	150
37	142	to	110	26	208	to	178

VARIATIONS FOR 100 MEN

Descending		Ascending	
Blood-pressure increased	27	Blood-pressure increased	24
Blood-pressure decreased	61	Blood-pressure decreased	65
Blood-pressure, no change	13	Blood-pressure, no change	11

Number of men whose blood-pressure increased both up and down	10
Number of men whose blood-pressure decreased both up and down	43
Number of men whose blood-pressure remained the same either way	3
Number of men whose blood-pressure was variable	44

It is of interest to compare our readings on the surface before descending with those of Thayer's for normal cases.

	Thayer's Cases	Our Cases	Difference
20 to 30 years	136.9	145.33	8.43
30 to 40 years	140.8	144.28	3.48
40 to 50 years	142.2	150.30	8.10
50 to 60 years	154.8	157.60	2.80

CONCLUSIONS

The rapid change in altitude, either up or down, was responsible for a fall in blood-pressure of approximately 5 mm.

Lower readings were obtained from the decade from 30 to 40 than from 20 to 30.

It was impossible to forecast by a man's build or any other factor what influence the ride would have on his blood-pressure.

It was demonstrated that after a day's work 1,700 feet below the surface the average blood-pressure was about the same as on the surface before starting to work.

It was demonstrated that abnormally high blood-pressure was not a contra-indication to hard work under ground.

Admitting that the standing position is responsible for an increase of from 4 to 8 mm., these readings show that there is little difference between sea level readings (Thayer's) and those taken a mile above the sea.

As factors influencing some of these higher readings, there must be taken into account the facts that the readings were taken in the standing position, that the men were, for the most part, heavy users of tobacco, tea and coffee, and moderate users of alcoholic beverages. Only one or two men seemed to be nervous at the time of the examinations.

SUPERPERMEABILITY IN NEPHRITIS*

WALTER A. BAETJER, M.D.
BALTIMORE

In a series of studies of renal function in the various clinical types of nephritis undertaken this year, I have been impressed by a striking peculiarity in the behavior to the functional tests of four cases,[1] all of which, clinically and from the urine examination, apparently belong to one group. The one feature characteristic to all has been a supranormal excretion of the substances employed in the functional tests in the presence of undoubted and severe renal disturbance.

In this connection it is interesting to note the recent article by Pepper and Austin,[2] in which these authors describe a case apparently of the same character as those here reported. The case cited was undoubtedly an instance of parenchymatous nephritis in which the phthalein test on one occasion showed an excretion of 71 per cent. for two hours, and two months later, 82 per cent. for the same time. There was, however, evidence of definite impairment of the chlorid elimination which has also been true in our series.

In our observations we have also studied the fluid balance, the elimination of lactose and potassium iodid (as described by Schlayer[3]) and the percentage of rest nitrogen in the blood-serum. The general response of these patients to all of the tests was essentially the same, and indicated in each instance, a condition of increased, rather than diminished permeability of the kidney, except as to the elimination of sodium chlorid. In spite of this apparently normal function there were other evidences of a severe grade of renal injury of the parenchymatous type.

It is unnecessary at this time to describe in detail the methods used in carrying out these tests, as they were in general similar to those described by Rowntree and Fitz[4] in their recent paper. Briefly, they were performed as follows:

Phthalein Test: According to the intramuscular technic of the original authors.[5]

Lactose Test: 2.5 gms. of lactose were dissolved in 25 c.c. of distilled water, pasteurized for four hours on four successive days and then injected intravenously.

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*From the Chemical Division of the Medical Clinic.
*Submitted for publication April 29, 1913.

1. These cases form a part of the whole group which will be reported in detail later.
2. Pepper and Austin: Am. Jour. Med. Sc., February, 1913, p. 254.
3. Schlayer: Deutsche. Arch. f. klin. Med., Dec. 28, 1910, ci.
4. Rowntree and Fitz: THE ARCHIVES INT. MED., 1913, ii, 258.
5. Rowntree and Geraghty: THE ARCHIVES INT. MED., 1912, xix, 284.

The excretion of this substance was tested qualitatively with Nylander's solution and also measured quantitatively by the polariscope. The normal time for excretion is from four to five hours (Schlayer).

Potassium Iodid Test: One-half gram was given by mouth, and the urine tested by Sandow's method. The completion of excretion within sixty hours is regarded as normal (Schlayer).

Rest Nitrogen Test: After precipitation of the proteins by alcohol, as described by Widal, the nitrogen in the filtrate was estimated by the Kjehldahl process. Normal serum so treated contains .4 to .6 gm. per liter.

A short history of the individual cases might be of advantage before considering them in detail with regard to their behavior toward the functional tests.

CASE 1.—Clinical Diagnosis: Chronic Nephritis.

A boy of 15 years complained of swelling of the face and legs. There was a past history of scarlet fever at the age of 2 years and some increased frequency of micturition in the past year.

His present trouble began one year before admission to the hospital with swelling of his face and legs which disappeared during the summer months and reappeared again in October, 1912.

Physical examination showed some puffiness of the eyelids and moderate edema of the ankles and feet. Otherwise the examination, including the eye-grounds, Wassermann and tuberculin reactions was entirely negative.

There was a moderate anemia with 4,000,000 R. B. C. and 50 per cent. Hbg. (Sahli).

The blood-pressure was 150 mm. (Tycos) on admission, but fell rapidly to 130.

The urine, during three weeks observation, showed constantly 7 to 12 grams of albumin per liter, with a moderate number of hyaline and granular casts; specific gravity 1.013 to 1.023; reaction acid.

There was no fever.

Functional Renal Tests: Phthalein was excreted to the extent of 75 per cent. after one hour, and 85 per cent. after two hours.

Lactose was detected only in specimens for the first two hours.

Potassium iodid was still being excreted after seventy-two hours.

The rest nitrogen of the serum was .33 gm. per liter.

The fluid balance was normal on an intake varying from 600 c.c. to 1,500 c.c. in twenty-four hours.

Sodium Chlorid: On an excess intake of 7 gm. he excreted but 2 gm. extra in the urine and gained 1½ pounds in weight in twenty-four hours.

CASE 2.—Clinical Diagnosis: Chronic Nephritis.

This patient was a man of 35 years, complaining of swelling of the feet and ankles. He had had the usual infections of childhood, including scarlet fever at the age of 11 years, but without any history of sequelae. For the past year he had noticed some increased frequency of urination.

The onset of his present symptoms occurred three weeks before his admission to the hospital with nausea and vomiting, marked dyspnea on exertion and edema of the feet, which had been increasing up to the time he applied for treatment.

The physical examination showed some edema of the face and rather marked swelling of the ankles and feet. His heart was of normal size and the liver not enlarged; in short, there was no evidence of broken compensation. The eye-grounds, Wassermann and tuberculin reactions were negative.

There was a moderate grade of anemia with 3,800,000 red blood-cells and 60 per cent. Hgb. (Sahli).

The blood-pressure was 190 mm. (Tycos) on admission, but fell rapidly to 140.

Cystoscopic examination was negative; phthalein appeared in seven minutes on both sides and the amount of urine was the same from each kidney, thus

excluding a unilateral lesion, possibly of a tuberculous nature, as was at first suspected. The urine during a period of two months showed 2 to 4 gm. of albumin per liter, with hyaline and granular casts, and occasionally a few red blood-cells. The reaction was acid, and the specific gravity 1.010 to 1.015.

There was a persistent fever varying between 99 and 101 F. for the first two weeks; after this the temperature remained normal until his discharge from the ward.

Functional Renal Tests: Phthalein was eliminated to the extent of 45 per cent. in each of the first two hours, making a two-hour total of 90 per cent.

Lactose was detected in the urine for six hours, which is generally given as the upper normal limit of time.

Potassium iodid was excreted for sixty-eight hours.

The rest nitrogen of the serum was .4 gm. per liter.

The fluid balance was normal on an intake from 1,000 to 1,600 c.c. per day.

Sodium Chlorid: On an excess ingestion of 7 gm. only 4 gm. extra were excreted, but there was no demonstrable gain in weight.

CASE 3.—Clinical Diagnosis: Bilateral pleurisy with effusion; acute arthritis; chronic nephritis.

The patient was a colored man, aged 22, who came to the hospital complaining of a cough, pain in the side, and swelling of the feet. His previous health had always been perfect until the onset of his present trouble, which began three weeks before with the symptoms enumerated above.

The physical examination revealed the presence of fluid in both pleural sacs, from which the pneumococcus was grown in pure culture. The heart was normal and the blood-pressure 115 mm. (Tycos). There was edema of both feet, more on the left, due to a coexisting acute arthritis of the left ankle.

The blood count showed 3,000,000 red blood-cells and 53 per cent. Hgb. (Sahli).

The temperature was irregularly elevated, varying between 100 and 104 F.

Examination of the urine showed the constant presence of albumin, persisting until the patient was discharged, two weeks after the fever had subsided. The amount, however, was not large as in the other cases. The specific gravity averaged 1.015 and there were a few casts present.

Functional Renal Tests: The phthalein test revealed an excretion of 72 per cent. for the first hour and 83 per cent. for two hours.

Lactose was excreted over a period of four hours.

The potassium iodid test was not done as the patient was receiving this drug medicinally.

The rest nitrogen was .18 per liter.

The fluid balance was good on an intake between 1,000 c.c. and 4,000 c.c.

Sodium Chlorid: On an excess intake of 7 gm., 3.4 gm. extra were excreted in the urine and the patient gained 2¼ pounds in twenty-four hours.

CASE 4.—Clinical Diagnosis: Chronic parenchymatous nephritis.

The patient, a girl aged 20, complained of swelling of the feet. Her health had always been excellent until the onset of her present symptoms, which followed an attack of so-called "grip," eight months previously, after which she first noticed the edema. The persistence of this symptom was her only complaint and was likewise the only striking feature revealed by examination. Her circulatory system and blood-pressure were normal. There was no fever.

The urine, over a prolonged period, contained from 7 to 10 gm. of albumin per liter; the sediment showed a few epithelial casts. Specific gravity, 1.010 to 1.020; reaction faintly acid.

Functional Renal Tests: The phthalein test revealed an excretion of 42 per cent. for the first hour and 69 per cent for two hours. The test, repeated two months later, showed 57 per cent. for the first hour and again 69 per cent. for two hours.

Lactose was demonstrable for but one hour. Repeated one week later, it was present for two hours, and again, two months later, it was positive for four hours. At the time of the last test the patient was definitely worse, showing a marked salt retention, with a steadily increasing edema.

Potassium iodid was excreted for forty-seven hours.

The rest nitrogen was .16 gm. per liter.

The fluid balance, at the time these studies were made, was normal on an intake from 1,000 c.c. to 1,800 c.c. per day.

Sodium Chlorid: On an excess intake of 10 gm. the excretion increased but 3.5 gm., and the patient gained 2 pounds in weight.

The brief outline of these cases given above will suffice to show their striking similarity, both in the clinical picture presented and in the general character of the urine. Furthermore, their behavior toward the various functional tests, particularly in the excretion of lactose and phthalein, was much the same. In all there was a remarkably good excretion of these substances in the presence of strong evidence of definite and possibly extensive renal changes.

Their similarity is further manifest in the uniform tendency toward poor elimination of sodium chlorid—a feature, also, of the case described by Pepper and Austin.[2]

While one would expect to find sporadic cases showing an anomalous excretion of any drug, the occurrence of four such examples in a comparatively short period of time (less than six months) would make one wonder whether this condition of such unusual permeability of the renal filter were present in a definite type of the disease, or whether it occurred at some stage in the various forms of nephritis. A third possibility, of course, would be that these cases offer only another example of the well-known hospital experience, that odd cases have a decided tendency to come in groups.

In considering the question of hyperpermeability, it must be recalled, of course, that many observers have called attention to the fact that in chronic parenchymatous nephritis the functional tests failed to give an adequate idea of the severity of the renal lesion. Bard,[6] and later Bard and Bonnet,[7] showed that the rapidity of elimination of methylene blue might be normal, or even exaggerated. Bernard[8] and Castaigne[9] also support this view; the former concluding that in the earlier stages of chronic parenchymatous nephritis, "dominated by the presence of edema and albuminuria, the renal permeability is normal, or even increased." "Later, after the disease has lasted for some time, the permeability becomes diminished." Dreyfus,[10] working with rosanilin, found that this dye behaved in a similar manner with regard to the rapidity of

6. Bard: Gaz. hebd. de méd., Paris, 1897, ii, 494.
7. Bard and Bonnett: Arch. gén. de méd., Paris, 1898, pp. 129, 283, 464.
8. Bernard: Thèse de Paris, 1900, pp. 104-147.
9. Castaigne: Thèse de Paris, 1900.
10. Dreyfus: Thèse de Lyon, 1898.

elimination, though the quantity secreted was, in his cases, less than normal. In studying the elimination of phthalein in these cases, Rowntree and Geraghty[11, 5] found no examples of any apparent hyperpermeability for this drug, although they were aware that it did exist for methylene blue and rosanilin. Sellards,[12] however, cites one case of parenchymatous nephritis in which the phthalein output was 79 per cent. for two hours.

A glance at the accompanying table will suffice to show that the phthalein elimination was well above normal in three out of the four

TABLE SHOWING WATER INTAKE AND OUTPUT AND THE EXCRETION OF VARIOUS SUBSTANCES IN THE AUTHOR'S CASES

	NaCl added to diet, Gm.	Water		NaCl Gm.	Lactose	KI	Phthalein, Per cent.			Rest Nitrogen Gm. Per Liter
		Intake	Output				1st hr.	2d hr.	Total	
Case 1	7	*780 *600	525 890	2.7 4.6	2 hrs.	72 hrs. +	75	10	85	.33
Case 2	7	1375 2420	825 1250	4.3 8.1	6 hrs.	68 hrs.	45	45	90	.4
Case 3	7	.....	1000 650	6 9.4	4 hrs.	Not given	72	11	83	.18
Case 4	7	1300	1250	2.4	1 hr.	47 hrs.	42	27	69	.16
					(1 week later) . 2 hrs.					
		1450	1400	6	(2 wks. later) 4 hrs.		(2 mos. later). 57	12	69	

*NOTE.—The upper figures in each case represent the average water intake and excretion and the NaCl excretion for the several days preceding the NaCl test. The lower figures are for the day on which the excess NaCl was given.

cases, and, in the fourth, was certainly well within the normal limits. Two of them showed a striking excretion of 72 per cent. and 75 per cent., respectively, in one hour — an excretion 20 per cent. higher than was found in any of the cases of parenchymatous nephritis reported,[5] and 10 per cent. higher than occurred in the normal cases,[5] in which the drug

11. Rowntree and Geraghty: Jour. Pharm. and Exper. Therap., 1910, vi, No. 4, 606-607.

12. Sellards: Johns Hopkins Hosp. Bull., October, 1912, p. 298.

was injected intramuscularly, as it was in these patients. The anemia present could hardly have had any influence, since it has been shown that in moderate grades there is no variation in the excretion of phthalein, whereas severe anemia tends to decrease the output.[5]

Rowntree and Geraghty, whose experience with the use of this test is far larger than my own, are equally at a loss to explain the supranormal excretion present in these cases, and it was at their suggestion that subcutaneous injections of tetra-chlor-phthalein (which is known not to be excreted by the normal kidney) was tried with the hope of demonstrating an increased permeability, if such were present. The test was unsuccessful, though it should be added that it was given in doses much smaller than what is now known to be the maximal amount tolerated by normal individuals without excretion in the urine.

The lactose test showed the same tendency toward an increased rapidity of excretion that was observed in the elimination of phthalein. The usual time for excretion, according to Schlayer,[3] is four to five hours, and occasionally six hours in rare cases. In three injections (see table) the time of excretion was well below normal; in two more it was just four hours, which is the lower limit of normal, while in only one was six hours required. This might possibly be interpreted as a slight delay. The percentage of excretion has been purposely not stated for the following reasons: In two of the early cases the total output was not determined, since Schlayer had emphasized chiefly the duration of excretion as giving the most valuable information. We have evidence, however (which will be brought out in a subsequent paper), which makes it seem probable that determinations of the total output are most essential in drawing proper conclusions from the test. Also there was some fever in two of the patients, which seems to influence the excretion, although Schlayer has apparently not found this to be the case. It might be mentioned, however, that in one test, in which the duration of excretion was only two hours, the output was 76 per cent., which, in comparison with the results in healthy people, is a good normal figure.

The results with the iodid test are most interesting. In two out of the three cases in which it was given, there was a definite delay in excretion, which, in connection with the impaired elimination of sodium chlorid, would seem to support Schlayer's view that the excretion of these two substances is the best index of tubular function. On the other hand, the excretion in the third case was complete at a time well inside the normal limit, while the NaCl elimination was similar to that in the other cases. It so happens that the subsequent course of this patient has indicated that the tubular destruction here was severer than in either of the others.

While it is true that the atypical response of a single isolated case is in no way conclusive, it gives definite evidence that the test is not infallible and adds support to the doubts as to its value, which were expressed by Rowntree and Fitz,[4] and in which, from experience with other cases (to be reported later), I quite concur: A possible explanation of this apparent anomaly is that in the very severe forms of tubular destruction the iodid tends to be suppressed rather than delayed.

The fluid balance and general response to increased NaCl ingestion may be appreciated from a glance at the accompanying table, and require but a word of explanation. Both factors were estimated daily until an approximate constant had been reached, and sufficient NaCl was given to avoid tissue starvation and possible chlorid retention from this cause. The tendency toward impaired salt elimination has been common to all cases and it has been the one test in these cases which gave evidence of functional renal impairment. This only serves to emphasize again the importance of determining the NaCl tolerance in edematous cases, a point which has been emphasized chiefly by Widal.

The principal features of resemblance in these cases, then, have been two:

1. Impaired elimination of NaCl.
2. Supranormal excretion of lactose and phthalein.

While it is true that these cases do not in any sense establish the fact that increased renal permeability can exist — and this explanation should be taken only as a suggestion — the observations at least indicate that there may exist either a definite type of nephritis in which the kidney is super-permeable to some of the substances used for the functional tests, as well as to serum albumin, or that this may be merely a transitory stage in certain types of nephritis.

This report is not, in any sense, to be interpreted as a criticism of functional kidney tests, but rather to emphasize the fact, already pointed out with regard to methylene blue by Bard, Bernard and others, that there are some cases at least, and possibly more than we have hitherto believed, in which certain functional tests may give entirely normal results in the presence of outspoken and serious renal changes. It has, of course, long been known that there may exist definite anatomical lesions of the kidney without evidences of impaired function. The cases here described, however, would indicate that there may be both definite anatomical lesions, as indicated by the urinary examination, as well as definite functional impairment, as shown by the deficient NaCl elimination, without disturbance in the excretion of other substances used in functional tests. Those who have worked most in this field have all encountered cases in which these tests revealed an elimination far better than the clinical examination would have led one to suspect. In these

instances it has usually been assumed that the high excretion following the functional tests justified a good prognosis, which may, of course, be true also in this series, for none of them has yet come to autopsy. It is also a well-recognized fact, clinically, that one occasionally sees a case with marked evidence of renal injury which goes on to apparently complete recovery. This question, however, only the future can decide. It is worth mentioning that two of these patients, who have been followed since, have shown no evidence, as yet, of any definite improvement in a period of three to four months.

In conclusion, it might be well to emphasize again some of the features which have been most striking in the study of these cases.

1. That there exist cases of well-marked nephritis with evidence of impairment of renal function in which certain tests reveal an eliminative power normal or even above normal.

2. That these cases may be more common than we have hitherto supposed, judging from an experience of four such examples in several months.

3. That the evidence from these suggests that there may exist in some types of nephritis a stage in which the kidney is hyperpermeable, at least to some substances used for functional tests, with an elective impermeability for chlorids as suggested by Widal.

4. That it is necessary to study renal function from the standpoint of a considerable series of functional tests rather than to draw conclusions from the excretion of any one drug.

It is a pleasure to thank Drs. Thayer and Barker for the interest taken in these cases and for allowing these studies to be made on the patients under their charge.

Johns Hopkins Hospital.

ACUTE UNILATERAL NEPHRITIS, WITH REPORT OF A CASE*

DAVID RIESMAN, M.D., AND GEORGE P. MÜLLER, M.D.
PHILADELPHIA

Synopsis of Authors' Case.—Woman, aged 22 years, seized with sudden pain in the left loin, radiating forward into the left hypochondrium; rigidity of lumbar muscles with tenderness in costovertebral angle; fever, rapid pulse; leukocytosis; in urine albumin, hyaline and granular casts, red blood-cells and pus-cells. Patient moderately septic; nephrectomy; kidney the seat of disseminated, suppurative nephritis. Patient made a good recovery although some weeks later it was necessary to remove the submaxillary gland for calculous inflammation.

Pathological and clinical studies have caused the belief to prevail that acute hematogenous inflammation of the kidney is always bilateral. This is, however, not the case; but exceptions to the rule are so rare and so little understood that reports of single instances are not without value. Acute unilateral inflammations differ from the commoner types of acute nephritis in that they are of an interstitial character; rather inflammatory than degenerative, and with a strong tendency to the formation of abscesses. Acute bilateral interstitial inflammation has long been known. It was found by Councilman[1] in scarlet fever, and has been seen in erysipelas, osteomyelitis, endocarditis, and pyemia. The infection in these cases is conveyed to the kidney by the blood-stream. Suppurative inflammation, pyelitis and pyelonephritis, is of course common in association with stone and tuberculosis. It is usually considered to be due to ascending inflammation, although this is by no means clearly established. In addition, there is a group of borderline cases, as, for instance, the pyelitis and pyelonephritis of pregnancy and the puerperium, in which it is difficult to say how the inflammation reaches the kidney. We are inclined to believe that even in these it is more likely to be hematogenous than an extension from below upward.

The particular type of unilateral nephritis to which we wish to refer in this communication is that which attacks a person apparently well, often without warning and with an unusually acute onset. In some patients the progress of the disease may be so rapid that in a few hours extreme prostration is observed, while in others the course may be protracted so that several days elapse before marked septic symptoms are noted. The patient complains of tense, throbbing pain in the loin, often radiating into the anterior aspect of the abdomen. There is tenderness

* Submitted for publication March 5, 1913.
* Read before the College of Physicians, Philadelphia, Nov. 6, 1912.

1. Councilman: Trans. Assn. Am. Phys., 1898, xiii.

over the same area, but most marked at the costovertebral angle, and this is accompanied by rigidity of all the muscles of the loin and of the oblique muscles of the abdominal wall. There is fever of variable degree with a correspondingly rapid pulse and a moderate leukocytosis. The urine is rather scanty in amount, of high color and turbid in appearance. It contains a considerable amount of albumin, and the sediment consists largely of casts, red blood-corpuscles and pus cells. Certain general manifestations such as headache, nausea and vomiting, delirium and even symptoms of uremia may appear and the patient looks and is extremely toxic.

In 1895, Weir[2] and Woodward[3] each reported cases of nephrectomy for unilateral suppurative nephritis, but the present surgical treatment of this affection is mostly due to the able teachings of Brewer,[4] who has persistently called attention to the subject, and in his latest contribution reports an experience of fourteen cases of the acute type and about a dozen of the mild type. Cobb[5] collected eight cases from the surgical wards of the Massachusetts General Hospital, all of them operated on since 1902. There are a few other instances recorded in the literature, and the number is increasing so that we shall soon become familiar with the affection and approach its diagnosis and treatment with more certainty and confidence.

CASE REPORT

The case that we have observed and of which we have given an epitome at the beginning of this article is as follows:

History.—Mrs. R. A. K., aged 22, had measles, mumps and scarlet fever when a child; in 1909 she had a severe attack of typhoid fever complicated with hemorrhages, but convalescence was not otherwise interrupted; she was quite well during the summer of 1910. Later she was married. During the early part of December, 1910, she suffered for two weeks from general aches and pains supposedly influenzal in origin, after which a vague pain persisted in the left loin, and she herself believed that some swelling was present, but her physician did not notice anything. December 23, she rode fourteen miles into the country in an automobile, the day being exceedingly cold. At 3 a. m. on December 24 she awakened nauseated and had an attack of vomiting; some hours later moderate pain in the left loin set in, and there was tenderness and rigidity; the temperature rose to 102 F. and the pulse to 120; the leukocytes on this day were counted and found to be 7,000, but two days later they had risen to 13,000. Daily examinations of the urine were made and showed it to be highly colored and to contain albumin and casts but no pus-cells. The attack gradually subsided, the pain and tenderness disappeared, but some rigidity persisted. December 30 she insisted on getting out of bed, following which act the symptoms recurred, and about this time it was noticed that pus was present in the urine. We saw her first on Dec. 31, 1910, at her home in the country.

2. Weir: Med. Rec., New York, 1895, xlvi, 325.

3. Woodward: Ann. Surg., 1895, xxi, 588.

4. Brewer: Surg., Gynec. and Obst., 1906, ii, 485; Ibid., 1908, vii, 699; Jour. Med. Soc. New Jersey, 1909, vi, 61; Yale Med. Jour., 1911, xvii, 237.

5. Cobb: Ann. Surg., 1908, xlviii, 680.

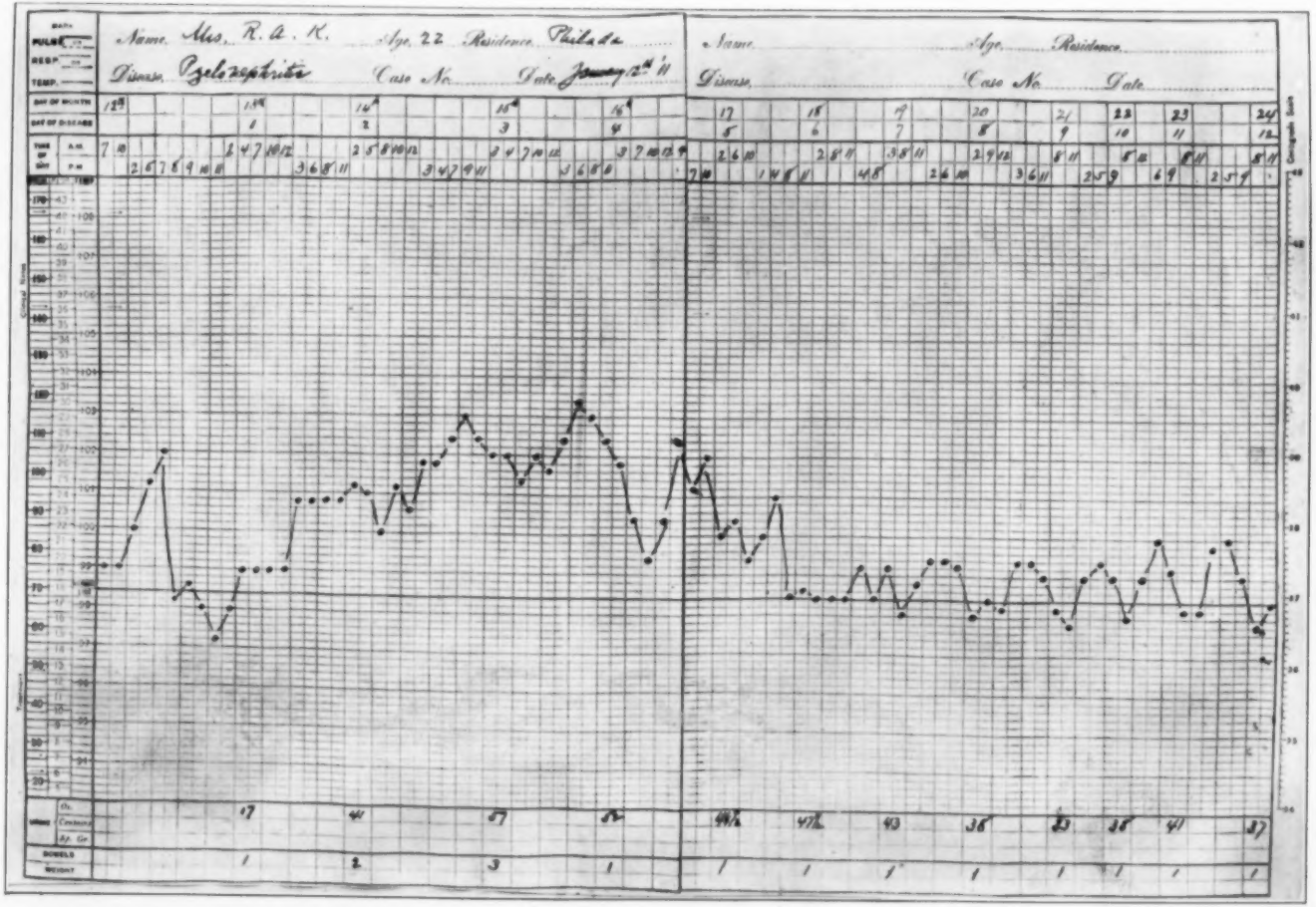
Name. Mrs. R. A. K. Age. 22 Residence. Phila da
Disease. Pyelonephritis Case No. Date. January 2nd '11
Name. Age. Residence.
Disease. Case No. Date.

Fig. 1.—Temperature chart after operation.

Examination.—We found a well-nourished, rather pale young woman, complaining of pain in the left loin and left hypochondrium, radiating at times down to the groin and sometimes to the back. Tenderness to pressure existed at the costovertebral angle and extended forward to the crest of the ilium. There was distinct rigidity of the muscles in the loin and a sense of fulness to palpation although no tumor could be detected. There was fever and a rapid pulse and a moderate leukocytosis, and urine analysis showed albumin, with hyaline and granular casts, erythrocytes and pus-cells in the sediment. The patient was not particularly prostrated, although she looked somewhat septic. We made a positive diagnosis of unilateral infection of the kidney. As she was a woman with abundant vitality and energy, we believed it would be safe to temporize a few days and await developments. Accordingly, hot fomentations were ordered for the kidney region, and hexamethylenamin (urotropin) and an abundance of water, liquid diet and purgation were prescribed. During the next ten days the patient varied in her condition, sometimes being on the verge of marked improvement, again having a relapse to the condition just mentioned. Finally, as the temperature continued around 102 F., and as her general appearance indicated an increasingly septic state, and as some delirium was manifested, an operation was deemed advisable. The symptoms were always unilateral and always located in the region of the left kidney. She was admitted to St. Agnes' Hospital January 11, 1911. During the few hours before operation the temperature ranged from 100 to 102 F.; the pulse from 84 to 100.

Operation.—The operation was performed Jan. 11, 1911, under ether anesthesia. The patient was placed in the usual lateral position over a kidney pillow and a curved incision was made downward and inward from near the costovertebral angle. On opening the deep fascia, the perinephric fat was found infiltrated and inflamed, bleeding with great readiness. On further exploration of the fat in the region of the kidney, an abscess was encountered containing 3 or 4 ounces of thick pus. The kidney was exposed and delivered with some difficulty and was found to be the seat of a diffuse, suppurative process. Accordingly, nephrectomy was performed and the wound packed with gauze and drained with a rubber tube. Partial closure of the wound was effected.

Examination of the specimen was made by Dr. Aller G. Ellis, Dr. John Speese, and ourselves, and the examination of the pus by Dr. Randle C. Rosenberger. The reports are as follows:

Macroscopic Description.—The kidney was about one and one-half times the normal size, intensely red and congested, with purple blotches of hemorrhage beneath the capsule. Near the lower pole a ragged opening existed with evidence of necrosis at its edges. In three other places rents were found, evidently caused by trauma during operation. It was afterward discovered that at the places hemorrhagic infarction existed. On section of the kidney the entire organ was seen to be intensely congested, especially the cortical portion, and to be the seat of numerous miliary abscesses. In the lower half, a large wedge-shaped yellow area communicated with the opening before mentioned and which had probably been made at the operation. The apex of the wedge represented the apex of a pyramid. One other such area, but somewhat smaller in size, was present. At the upper pole a round, orange-colored mass about 4 mm. in diameter was discovered; it was thought to be tuberculosis but was found on microscopic examination to be a hypernephroma.

Microscopic Description.—Sections show a hemorrhagic fibrinocellular exudate on the surface of the renal capsule. At several points a large amount of hemorrhage is present and exists as an infarct. The capsular vessels are dilated and a diffuse leukocytic infiltration begins beneath the capsule and extends downward through the cortex and medulla. Many of the leukocytes are of the polynuclear form. The renal epithelium shows degenerative changes and cloudy swelling with numerous casts. The stroma in some areas is decidedly fibrous.

There was no evidence of tuberculosis in any of the sections examined by Dr. Speese, Dr. Ellis or ourselves. In the specimen submitted to Dr. Ellis a small hypernephroma was discovered, with extensive connective tissue formation.

Postoperative History.—The patient reacted from the shock in a few hours; afterward the temperature gradually rose until on the fourth day it was 103 F.; then it slowly declined to the normal, which was reached on the sixth day after operation. The pulse remained high, rapid and weak for several days. The patient commenced to pass urine shortly after the operation and during the first twenty-four hours 17 ounces were excreted. During the second twenty-four hours 41 ounces and during the third 57 ounces were voided. The amount of urine during the first ten days after operation varied from 33 to 57 ounces, and averaged 44 ounces, and during the last ten days of her stay in the hospital, it varied from 31 to 46 ounces, and averaged 39 ounces. At first there was abundant albumin with casts, pus-cells and erythrocytes, but the sediment gradually lessened and for the last week examination was negative for albumin, casts and pus. The last urinalysis showed a specific gravity of 1.010. The gauze packing was removed from the wound during the second week, but con-

Fig. 2.—Section through capsule and cortex, showing great thickening of the former, with fibroid change, hemorrhage, and round cell infiltration; pronounced cellular infiltration of superficial layers of cortex.

siderable wound trouble was experienced which protracted convalescence. A bacteriologic examination of the pus in the kidney removed at operation, and later of the wound discharge, revealed the *Micrococcus pyogenes aureus* and from the culture a vaccine was made by Dr. Rosenberger and administered several times to the patient. The examination of the blood showed hemoglobin 38 per cent. on the day after operation and from this it hardly varied until February 14, when it began to rise steadily. The first count of red blood-cells made four days after operation revealed 3,200,000 and the count varied but little from this until February 14, when it showed 3,940,000, after which continued improvement took place. The leukocytes varied, depending on the condition of the wound, but averaged about 13,000 during her stay in the hospital.

The patient was discharged February 25, 1911, forty-four days after admission, with a small sinus rapidly closing. Her general health was excellent, although some weakness persisted. The sinus healed entirely in one week. About six weeks later, the patient complained of swelling, pain and tenderness beneath the right lower jaw and noticed some salivation with a foul odor and salty taste in the mouth. An examination revealed a swelling of the right submaxillary salivary gland, densely hard in character, not acutely inflammatory but somewhat tender to pressure. Pressure caused pus to exude from the duct of Wharton into the mouth. A radiograph made by Dr. Pancoast showed the presence of a calculus.

Under ether anesthesia a 2-inch incision was made beneath the jaw and the submaxillary salivary gland removed. It contained an oval calculus about 12 mm. in length. Since this time, the patient has been perfectly well, gaining in weight and strength and frequent urinalyses have shown nothing abnormal. Later she became pregnant; nothing unusual happened until October 27, when a miscarriage occurred. The patient suffered no ill effects from this, however. On November 1, she was passing 40 ounces of urine in the twenty-four hours, with a specific gravity of 1.015 and showing nothing abnormal to chemical or microscopic examination.

ETIOLOGY

The kidney in unilateral nephritis may become infected in one of three ways:

1. *By an Ascending or Urogenous Infection.*—This is much less common than was once held, and Sampson's[6] well-known paper, pub- in 1903, states the case correctly in the following words:

The reflux of urine from the bladder into the ureters may be considered an etiologic factor in the causation and maintenance of renal infection only when the intravesical portion of the ureter is diseased, thus impairing its function, or when some ureteral abnormality exists.

It is thus seen that the kidney is protected from ascending invasion by the downward current of urine and the physical condition of the healthy ureteral orifice. Of course, infection may be transmitted to the pelvis of the kidney by an unclean ureteral catherization.

2. *Lymphatic Infection.*—A local spread of infection from the intestinal tract or from the lower urinary organs by way of the lymphatics is not common, but does sometimes occur. Some interesting experimental work has been published recently by Kunita,[7] showing the way in which the lymphatics of the ureter communicate with those of the perinephric tissue and kidney, and by Franke,[8] who found that the ascending colon and cecum were connected by a chain of lymphatics with the right kidney but was unable to find such connection in the case of the left kidney.

3. *Hematogenous Infection.*—This is the common mode. It is well known that micro-organisms frequently pass through the kidney without injuring it in so far as we know. The urine swarms with typhoid bacilli in many cases of typhoid fever and one frequently observes a colon bacil-

6. Sampson: Bull. Johns Hopkins Hosp., 1903, xiv, 334.
7. Quoted by Stewart: Univ. Penna. Med. Bull., 1910, xxiii, 233.
8. Franke: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1911, xxii, 623.

luria; although in neither case are symptoms of kidney infection necessarily present. There has been some experimental work published indicating that the passage of micro-organisms through the kidney is always attended by damage histologically, although clinically no trouble may be appreciable. It has also long been known that by experimentally tying the ureter, bruising the kidney and injecting cultures of staphylococci into the veins, the kidneys will become infected. These infections point the way to an understanding of the workings of well-known clinical conditions as factors in the etiology of pyelonephritis. Most cases of pyelonephritis are probably unilateral in the beginning. Theoretically, a source of infection must exist somewhere in the body, although it

Fig. 3.—Section through cortical portion of kidney showing intense intertubular and periglomerular round cell infiltration.

is not always easy to ascertain the source. In view of the fact that the colon bacillus is the most frequent cause of urinary infections, we may reasonably infer that intestinal stasis, intestinal ulceration and severe and long-continued constipation act as predisposing factors. Previous infections, such as furuncle, tonsillitis, tooth abscesses or any form of peripheral suppuration may predispose to pyelonephritis. The bladder, the prostate gland and the uterus and its appendages may also act as portals of entry, and certain general conditions of which typhoid fever and influenza are the most prominent examples may contribute to hematogenous infection of the kidney.

In addition to the entrance of infection, there must be some cause, traumatic or otherwise, operating to reduce the resistance of the renal tissue. This, likewise, is not always easily determined. Many of the cases reported as acute unilateral pyelonephritis with suppuration have occurred suddenly in an apparently normal kidney of persons previously well, and the infecting agent was usually the colon bacillus or the *Staphylococcus aureus*. It may be that these organisms were highly virulent or in excessive number, or it may be that some unrecognized abnormality of the kidney was present. A few years ago, Kidd[9] suggested that as the majority of cases occur in women and involve the right kidney, undue mobility of the organ may be a predisposing factor, and Cotton[10] reports two cases in which there was a definite displacement of the infected (right) kidney. The micro-organisms usually found in pyelonephritis are the *Bacillus coli communis*, *Micrococcus aureus*, *Streptococcus*, and the typhoid bacillus. The great majority of cases have occurred in women, and the only explanation would seem to be the more frequent displacement of the right kidney and the greater tendency to intestinal stasis in that sex.

Recently unilateral renal hemorrhage of apparently unknown origin and sometimes called essential hematuria, has been placed in the group which we are discussing and considered to be of bacterial origin. Thus, Gaudiana[11] concludes that with the exception of early tuberculosis, lithiasis, neoplasms, torsion of the pedicle or Bright's disease, all cases described as hemorrhagic nephralgia are cases of unilateral nephritis and are the result of bacterial invasion of the kidney. Acute hematogenous infection is also of interest in connection with the pyelitis of pregnancy, but any discussion of this disease would occupy more space than the limit of our paper permits. Louria,[12] in a recent paper has given some consideration to the subject. Brewer's[13] conclusions regarding the etiology are important and may be quoted:

> During the progress of any infectious disease a certain number of micro-organisms find their way into the blood current; many of these organisms are excreted through the kidneys. If their number is comparatively small, if their virulence is low, and if the kidneys are in a healthy condition, the transit of these organisms through the renal apparatus gives rise to no demonstrable lesion. If, on the other hand, the number of the organisms is large, if their virulence is high, or if one or both kidneys are diseased, lesions are produced which may at the onset cause an overwhelming and fatal toxemia, or may proceed more slowly to the development of any of the classical types of renal infection or suppuration. While the disease may be bilateral, in a large number of instances it is unilateral and its unilateral character is due to the fact that

9. Kidd: Urinary Surgery, 1910.
10. Cotton: Ann. Surg., 1911, liv, 577.
11. Gaudiana: Folia urologica, 1908-1909, iii, 570.
12. Louria: New York Med. Jour., 1911, xciii, 1073.
13. Brewer: Jour. Am. Med. Assn., 1911, lvii, 187.

the affected kidney has lost to some extent its normal resistance to infection, by reason of trauma, abnormal mobility, previous disease, calculous irritation, anemia, passive hyperemia, complete, incomplete or intermittent hydronephrosis. The presence in the body of a kidney damaged by trauma or disease to such an extent as to lower its normal resistance to infection is a distinct menace to the individual, in that it possesses a potential susceptibility toward even the mildest forms of blood infection. While it is possible to produce renal lesions in animals by means of the *Bacillus coli*, the *Streptococcus pyogenes*, the *Staphylococcus pyogenes aureus*, the *Bacillus typhosus*, the pneumococcus, and the pyocyaneus, in clinical cases only the first four of these organisms have been isolated.

PATHOLOGY

The macroscopic appearance of the kidney varies with the stage of advancement of the morbid process. At first the kidney is swollen, tense

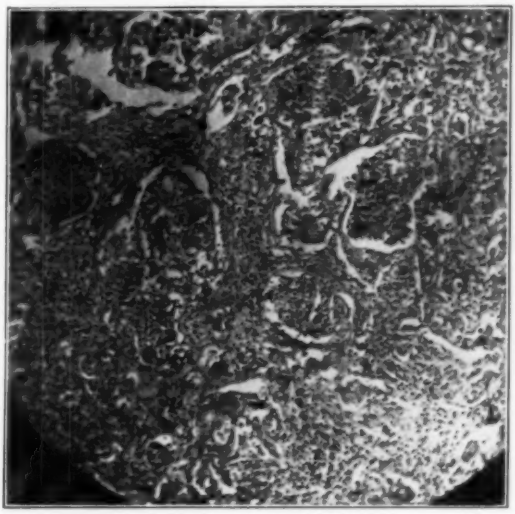

Fig. 4.—Section through cortical portion of kidney showing moderate amount of cell infiltration, edema, degenerative changes in glomeruli and tubules.

and engorged with blood, and distinct infarcts may be seen. Later, numerous yellow nodules appear beneath the capsule surrounded by a zone of intense congestion. On section, these nodules are found to be the bases of wedge-shaped areas of suppuration in the cortex. Long linear yellow streaks may indicate suppuration in the tubules. The microscopic changes consist of a diffuse congestion and leukocytic infiltration with numerous foci of suppuration; there is often much hemorrhage beneath the capsule, and throughout the cortex triangular infarcts, hemorrhage and suppuration may be present. Large bacterial masses looking like emboli are often seen. In the later stages the foci of suppuration coalesce

and gross abscesses may be formed. The Malpighian tufts are congested and usually surrounded by leukocytic infiltration. The pelvis is congested and covered with exudate.

SYMPTOMS

The clinical picture of hematogenous pyelonephritis varies considerably with the virulence of the process. Brewer describes three types: 1. The severe type, in which the local symptoms are obscured by an intense toxemia, and a fatal result occurs unless the infected kidney is removed. 2. The intermediary type, with severe initial symptoms, but without grave toxemia. Renal abscess, perinephritic abscess, pyelonephritis or pyonephrosis develops in neglected cases. The symptoms may simulate appendicitis, cholecystitis, or abscess of the liver, and, if the renal disturbance is not marked, may resemble typhoid fever or pneumonia. 3. The mild type, with tenderness over the costovertebral angle as the only symptom, suggesting subacute appendicitis or cholecystitis. Brewer believes that this type accounts for certain irregular periods of temperature occurring during convalescence from some surgical conditions or infectious diseases. 4. To these we will add a fourth type, that in which the chief and perhaps the only symptom is hematuria. We have referred to the observations of Gaudiani and would also add those of Eshner,[14] Billings,[15] Elliott,[16] and White[17] for additional support of the view that some of the so-called "essential hematurias" are due to bacterial invasion of the kidney.

The "severe" type of Brewer or the fulminating type of other writers is of sudden onset in a person apparently well. There is severe abdominal pain, tenderness, rigidity, nausea and vomiting. While the pain at times is characteristic of renal disease, it generally suggests some intraperitoneal process on the side affected, usually of the stomach, gallbladder or appendix. A number of the cases reported in the literature were operated on for appendicitis, cholecystitis or perforated duodenal ulcer before the true condition was recognized. The temperature rises sharply, even as high as 106 F., and there may be a chill or succession of chills. Septic symptoms develop and sometimes death may ensue before any distinctive renal or urinary signs are observed. As a rule, however, an indication of the true condition of affairs is given by the shifting of the pain to the flank and the finding of a point of more or less severe tenderness at the costovertebral angle. It is rare that the enlarged kidney can be palpated owing to the rigidity present, although some resistance may be felt by bimanual examination. The urinary findings

14. Eshner: Am. Jour. Med. Sc., April, 1903.
15. Billings: Am. Jour. Med. Sc., 1910, p. 625.
16. Elliott: Internat. Clinics, IV, 1906, 16th series, p. 122.
17. White: Quart. Jour. Med., 1911.

during the early hours are inconclusive and do not differ from those in any other severe septic infection, but later the urine becomes scanty and contains albumin, casts, blood and pus cells and the pathogenic micro-organism in pure or mixed culture. There is usually a high degree of leukocytosis and headache, muscular twitchings, convulsions or delirium may be present. The fatal termination is due to a combination of sepsis and uremia.

The second type, the *forme aigue* of Albarran, resembles the foregoing except that the intense septic symptoms are absent. More time is given in which to make a diagnosis, and the costovertebral tenderness and the urinary findings may be supplemented by ureteral catheterization. The bladder is seen to be intensely inflamed about the ureteral orifice,

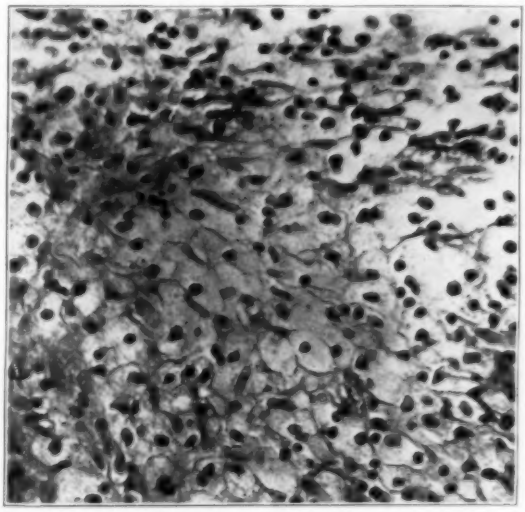

Fig. 5.—Section through small white nodule in cortex of kidney, showing character of the so-called hypernephroma.

from which pus may be seen exuding, and the lips of the orifice are edematous and pouting, and often ulcerated. The cystoscopic examination should not be undertaken during the acute attack, unless nephrectomy is contemplated. An x-ray examination should be made to determine the presence or absence of calculus.

The mild type which Brewer also terms "idiopathic pyelitis" has but few symptoms except moderate pain (backache) and costovertebral tenderness. A trace of albumin and a few casts, blood-cells and pus cells will be found in the urine. Some of these cases have no doubt been operated on for subacute appendicitis or cholecystitis; on the other hand,

they may account for "certain irregular periods of temperature occurring during convalescence from some surgical condition or infectious disease" (Brewer). The fourth type is characterized by persistent hematuria, which cystoscopy shows to come from one kidney, and the cause of which is revealed only at operation.

Treatment.—The acute fulminating form should be operated on as soon as the diagnosis can be made, with the intention of performing nephrectomy, unless nephrotomy with drainage will suffice. In 1911, Brewer reported that he had encountered fourteen cases of the severe type; two patients were untreated, and in four nephrotomy and drainage was done; they all died. Eight were treated by early nephrectomy and all recovered. The general statistics on the subject are not yet susceptible of analysis. It is quite true that the fulminating type sometimes subsides without operation; but just as in acute appendicitis, we never know which cases will recover and which will not. Of greater importance is the question of whether to do a nephrectomy or a nephrotomy. Brewer and Cobb have obtained splendid results from nephrectomy, but there is much to be said for the less radical procedure, chiefly because of the uncertainty as to the condition or even the presence of the other kidney, since there is rarely time for a cystoscopic examination. The objections that have been urged against nephrotomy are the inability to drain the whole organ by splitting it and the subsequent uselessness or even the menace of a kidney riddled with abscesses. Cases are on record in which the symptoms recurred after nephrotomy, necessitating a subsequent nephrectomy. In the subacute types, more time is given for investigation of the other kidney and the diseased organ can be more successfully treated. In the case herein reported we adopted a conservative plan of treatment for nearly three weeks, and when forced to operate we did a nephrectomy, because the friable, disorganized state of the kidney forbade a nephrotomy. Of course, in the mild cases operation is not to be thought of; rest in bed, a milk diet, urinary antiseptics, purgatives and plenty of water will usually bring about a cure. In refractory cases, bacterins should be used, and in persistent pyelitis it may be necessary to irrigate the renal pelvis through a ureteral catheter with a solution of one of the silver salts or with a 2 per cent. solution of aluminium acetate. If still resistant, it is advisable to operate — to split the capsule and drain the renal pelvis. In all such cases the existence of pressure on the ureter or of movable kidney should be investigated.

THE EFFECT OF URANIUM NEPHRITIS ON THE EXCRETION OF CREATININ, URIC ACID AND CHLORIDS, AND THE EFFECT OF CREATININ INJECTIONS DURING URANIUM NEPHRITIS *

WALTER M. KRAUS, M.D.
NEW YORK

I. INTRODUCTION

The experiments described in this paper were begun with the intention of determining the effect of uranium nitrate on the excretion of creatinin by the kidney, and the effect of creatinin injections on the nephritis produced by uranium nitrate. Chlorids were estimated in the last three experiments to check up the results with creatinin. Uric acid estimations were added, as it was found that no work had been done on the subject. The work was begun in the winter of 1911, during the writer's second year at the Johns Hopkins Medical School, but was not successful at that time. The experiments described below were conducted in this laboratory during the two succeeding summers of 1911 and 1912.

II. EXPERIMENTAL

A. Methods.—Dogs which had not previously been used for any experimentation were taken. They were kept in cages of the type described by Dr. Gies.[1] The urine was collected daily at 8:30 a. m. Powdered thymol was used as a urinary preservative. The cages were carefully cleaned each morning.

The dogs were fed on uniform quantities of hashed lean beef, cracker-meal, lard and distilled water in a homogeneous mixture. Bone ash was added to the food to insure the elimination of formed feces, which were found except when stated to the contrary in the protocols. The dogs were fed regularly at 9 a. m.

A word must be said here concerning the meat included in the diet. The amount was always small—15 grams. Closson,[2] Klercker[3] and Lefmann[4] have shown that muscle as food does not increase urinary crea-

* Submitted for publication April 9, 1913.

* From the Biochemical Laboratory of Columbia University, at the College of Physicians and Surgeons, New York City.

1. Gies, W. J.: Am. Jour. Physiol., 1905, xiv, 403.
2. Closson: Am. Jour. Physiol., 1906, xvi, 252.
3. Klercker: Beitr. z. chem. Physiol. u. Pathol., 1906, v, No. 8, p. 59.
4. Lefmann: Ztschr. f. physiol. Chem., 1908, lvii, 476.

tinin; and furthermore, it has been noted by Underhill and Kleiner[5] that there is no decrease in dogs in urinary creatinin during a fast of ten days. These observations warrant the belief that the absence of so small an amount as 15 grams of meat, during refusal of food by the animals, could not have made any difference in the output of urinary creatinin.

Intravenous injections were made from a buret through a small cannula into a saphenous vein. A very small quantity of 2 per cent. cocain solution was used as a local anesthetic.

The subcutaneous injections were made in the skin of the back or hind leg.

The creatinin was estimated by Folin's[6] method, the uric acid by the Folin-Shaffer[7] method; the chlorids by Harvey's[8] method; albumin with Tsuchaya's[9] reagent using Esbach tubes. The urines were analyzed as soon as collected.

B. Lesions Caused by Uranium Nitrate.—The acute renal lesions caused by uranium nitrate have been shown to be the same by all investigators except two. These lesions consist in general of a severe tubular injury combined with a vascular change, the latter of which has been demonstrated by physiological, but not by anatomical observations.

As to the tubular lesions, Pearce[10] states that "the anatomical changes due to uranium and to the chromates are in the early stages confined essentially to the tubules, especially the convoluted tubules, and consist of granular or fatty degeneration and definite necrosis often affecting large groups of tubules." This is in essence what has been found by Schlayer and Takayasu,[11] Schlayer, Hedinger and Takayasu,[12] Pearce, Hill and Eisenbrey,[13] MacNider,[14] Pohl,[15] Christian,[16] and Heineke and Meyerstein.[17] As to the vascular changes, Chittenden and Lambert[18] showed as early as 1889 that uranium in its early action on the kidney caused an increased urinary volume which, when the toxic action became more decided, changed to a partial or complete stoppage of urinary secretion. Schlayer states that the serious disturbances of the integrity of the renal vessels shown by functional investigation in uranium nephritis are not recog-

5. Underhill and Kleiner: Jour. Biol. Chem., 1908, iv, 165.
6. Folin, O.: Ztschr. f. physiol. Chem., 1904, xli, 223.
7. Folin and Shaffer: Ztschr. f. physiol. Chem., 1901, xxxii, 556.
8. Harvey, E. C.: THE ARCHIVES INT. MED., 1910, vi, 12.
9. Tsuchaya: Centralbl. f. inn. Med., 1908, xxix, 105.
10. Pearce, R. M.: Harvey Lectures, 1909 and 1910.
11. Schlayer and Takayasu: Deutsch. Arch. f. klin. Med., 1910, xcviii, 17.
12. Schlayer, Hedinger and Takayasu: Deutsch. Arch. f. klin. Med., 1907, xci, 59.
13. Pearce, Hill and Eisenbrey: Jour. Exper. Med., 1910, xii, 196.
14. MacNider: Jour. Pharmacol. and Exper. Therap., 1912, iii, 423.
15. Pohl: Arch f. Exper. Path. u. Pharmacol., 1912, lxvii, 233.
16. Christian, Smith and Chandler: THE ARCHIVES INT. MED., 1911, viii, 468.
17. Heineke and Meyerstein: Deutsch. Arch. f. klin. Med., 1907, xc, 101.
18. Chittenden and Lambert: Ztschr. f. Biol., 1889, xxv, 513.

nizable from the anatomical picture. These disturbances Schlayer, Hedinger and Takayasu[12] showed to be an initial increase in the dilatability and contractibility of the blood-vessels of the kidney and an increased permeability followed, in a day or two, by a reversed condition (Fig. 1). Pearce, Hill and Eisenbrey[13] confirmed this. Pohl,[15] working on rabbits with very small doses of uranium nitrate (0.035 mg.), produced a subacute nephritis, which exhibited, physiologically, a polyuria reaching its height in a week or ten days; and showed, anatomically, at the end of two weeks, that the glomeruli were intact, but that the tubular epithelium was flattened or entirely destroyed. MacNider,[14] and Heineke and Meyerstein[17] found engorgement of the intertubular vessels and of the glomerular capillaries.

As further proof of the tubular lesion Eisenbrey,[19] found that phenolsulphonephthalein is often excreted in increased amounts in the first twenty-four hours of uranium nephritis and always is excreted in

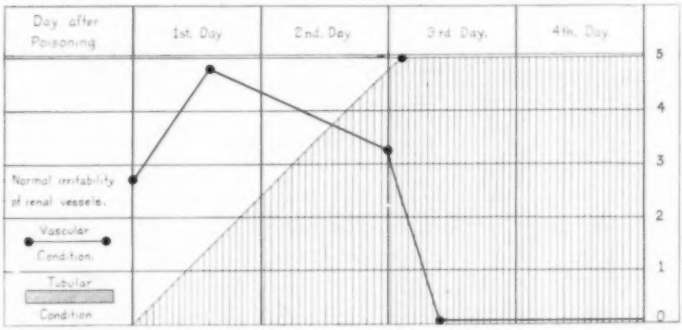

Fig. 1.—Effect of uranium on the kidney. 1. Faint spot-like clouding. 2. More diffuse clouding and spot-like necrosis. 3. Wider areas disturbed. 4. More widely-spread disturbance. 5. Practically no normal tubules remain.

decreased amounts thereafter. In view of the statement of Rowntree and Geraghty,[20] "that experimental evidences indicate that phenolsulphonephthalein is excreted mostly by the tubules," the work of Eisenbrey becomes confirmatory evidence of what has been said above concerning the lesions of uranium nephritis; that is, that uranium nitrate produces a vascular reaction of one or two days' duration followed by a tubular disturbance of wide extent. Christian pointed out that in addition to the tubular lesion "there occurs in the glomeruli a degenerative condition consisting usually of the appearance of hyaline droplets of varying size in the wall of the capillary." MacNider states that similar structures have been observed in several of his experiments. He also notes that

19. Eisenbrey: Jour. Exper. Med., 1911, xiv, 462.
20. Rowntree and Geraghty: The Archives Int. Med., 1912, ix, 284.

TABLE 1.—Creatinin Injections and Acute Nephritis

Experiment 1.—Diet: water, 400 c.c.; meat, 15 gm.; cracker-meal, 75 gm.; lard, 35 gm.; bone ash, 8 gm.

Date	Weight Kilos	Temp. F.	Urine				Feces	Remarks
			Vol., c.c	Sp. gr. 10 xx	React. Litmus	Creatinin, Mg.		
July 21-22	8.40	101.2	250	19	Acid	...	..	
July 22-23	8.33	101.6	240	13	Acid	235	..	
July 23-24	8.27	101.6	275	11	Acid	203	..	
July 24-25	8.33	101.6	245	10	Acid	172	..	
July 25-26	8.25	102.0	330	10	Acid	237	..	
July 26-27	8.24	102.0	345	08	Acid	186	..	
July 27-28	8.31	102.0	305	08	Acid	265	..	
July 28-29	8.28	101.8	250	10	Acid	146	..	
July 29-30	8.36	101.8	190	14	Acid	226	..	
July 30-31	8.31	101.8	...	..	Acid	...	+	
July 31-Aug. 1	8.31	101.8	285	11	Acid	190	+	
Aug. 1-2	8.34	102.4	200	..	Acid	360	+	Feces admixed.
Aug. 2-3	8.34	101.8	280	08	Alk.	090	+	
Aug. 3-4	8.34	101.8	315	14	Acid	340	+	0.1056 gm. creatinin injected intravenously 10:40 a. m. 20 c.c. saline.
Aug. 4-5	8.24	102.4	...	..	Acid	...	+	Foamy vomitus.
Aug. 5-6	8.26	101.8	345	10	Acid	321	+	
Aug. 6-7	8.30	102.0	280	10	Acid	224	+	
Aug. 7-8	7.80	101.4	375	17	Acid	202	+	0.1087 gm. creatinin injected intravenously 10:40 a. m. 20 c.c. saline. Vomited after operation.
Aug. 8-9	8.15	100.8	190	25	Acid	421	—	
Aug. 9-10	8.27	102.2	205	07	Acid	114	+	
Aug. 10-11	8.27	102.2	300	08	Acid	216	—	
Aug. 11-12	8.22	102.3	265	11	Acid	222	+	
Aug. 12-13	8.20	102.2	340	10	Acid	205	+	
Aug. 13-14	8.20	102.6	285	10	Acid	210	+	
Aug. 14-15	8.17	102.4	275	15	Acid	317	+	0.1012 gm. creatinin injected intravenously. 10:10 a. m. 18.8 c.c. saline. Vomited after operation. Vomitus taken at 3:45 p. m.

Aug. 15-16	8.12	102.5	290	11	Alk.	234	+	Vomitus foamy only.
Aug. 16-17	8.20	102.5	160	10	Alk.	120	+	
Aug. 17-18	8.24	102.3	215	10	Alk.	192	—	
Aug. 18-19	8.17	102.8	312	10	Alk.	243	+	
Aug. 19-20	8.16	102.7	460	10	Alk.	369	+	Injected 0.1000 gm. creatinin intravenously 4:30 p. m. 20 c.c. saline.
Aug. 20-21	8.16	102.5	255	07	Alk.	107	+	
Aug. 21-22	8.23	102.4	275	11	Alk.	327	+	
Aug. 22-23	8.27	102.3	235	12	Alk.	105	—	
Aug. 23-24	8.12	103.8	331	..	Alk.	281	+	Slight diarrhea, 10 mg. uranium subcuta. 5:13 p. m.
Aug. 24-25	7.73	102.3	681	..	Alk.	228	—	Some food not taken.
Aug. 25-26	7.60	102.2	420	..	Acid	114	+	All food refused.
Aug. 26-27	7.48	100.6	*	..	Acid	21	+	All food refused. Injected 0.1067 gm. creatinin intravenously 4:30 p. m. 20 c.c. saline.
Aug. 27-28	7.13	100.6	*	..	Acid	0	+	All food refused. Apathetic, weak, does not respond to calls.
Aug. 28-29	.7.02	.....	*	..	Acid	0	+	All food refused. Same. Right eye has purulent discharge, feces bloody.
Aug. 29-30	6.94	.....	130	..	Acid	0	+	All food refused. Same. Left eye involved also, feces bloody.
Aug. 30-31	6.82	98.8	72	..	Acid	0	+	All food refused except 400 c.c. aq. Same. Irregular contractions of masseters and intercostal muscles. Occasional spasm of fore paws. Cannot stand steadily. Subcutaneous edema. Feces bloody.
Aug. 31-Sept. 1	6.77	95.0	275	..	Acid	0†	+	All food refused except 400 c.c. aq. a. m., weaker. Complete spasm of fore legs. Partial of rear. Cannot stand. Feces bloody. p. m., dyspnea marked. Other conditions worse. Rear legs spastic now. Died in convulsions at 3:30 p. m.

* Total three days 280 c.c. Average each day 96 c.c.
† No creatin present.

different animals vary greatly in their response to the same quantity of poison per kilo. This has been found to be the case in my own experiments also.

The accompanying chart taken from the article of Schlayer and Takayasu (p. 615) shows graphically what has been stated above.

The lesions produced in my experiments, so far as concerns acute nephritic conditions aggravated by injections of creatinin, were essentially the same as those in the cases mentioned above. In the gross, the kidney was enlarged, the capsule tense; microscopically, the tubular epithelium (mainly of the convoluted tubules) was swollen, sometimes occluding the lumina, and showed granular degeneration and necrosis. The nuclei, especially in the convoluted tubules, could not be made out in most of the cells. The glomeruli were intact. Bowman's capsule was distended in many instances and the intracapsular space was partially filled with a granular material. There was no proliferation of the epithelium of the capsule. The blood-vessels were much engorged.

The kidney in Experiment 3, which was examined two weeks after uranium had been injected four times during twenty-two days, showed a somewhat different picture. Macroscopically, the kidney was swollen. The capsule was tense and not adherent. The surface was smooth. Microscopically, the lesions were mainly tubular. There were not as many injured tubules visible as in the other cases, but those which were injured seemed more severely affected. In many instances the cells had entirely separated from the basement membrane and lay as an ill-defined granular mass in the lumina. In other instances, practically normal tubular epithelium could be seen. The glomeruli showed thickening of Bowman's capsule in several instances and in a few places there was round-cell infiltration about the capsules.

C. Polyuria.—There is almost unanimity of opinion that polyuria occurs in the early stages of uranium nephritis. Chittenden and Lambert[10] noted it in 1889. Since then, Schlayer and Takayasu,[11] Pearce, Hill and Eisenbrey,[13] Schlayer, Hedinger and Takayasu,[12] and MacNider[14] have observed this same reaction. As stated above, this reaction has not been definitely associated with pathological lesions. The recent work of MacNider[14] and of Pohl[15] shows that with small doses of uranium nitrate, this vascular reaction may persist for more than the one or two days stated by the investigators named above.

It is interesting to note that MacNider[14] differentiates between anuric and polyuric animals and states that, though the vascular lesions are identical in these two groups, the tubular involvement differs markedly. In the anuric group this consists in swollen epithelium which occludes the tubular lumina, while in the polyuric group no epithelial involvement is present.

TABLE 2.—Acute Nephritis and Creatinin Injections

Experiment 2.—Diet: water, 500 c.c.; meat, 15 gm.; cracker-meal, 75 gm.; lard, 35 gm.; bone ash, 8 gm.

Date	Weight, Kilos	Urine							Feces	Remarks
		Vol. c.c.	Sp. Gr. 10 xx	Reaction, Litmus	Creatinin, Mg.	Uric Acid, Mg.	Chlorids Gm.	Albumin, Gm.		
July 23-24	8.82	460	05	Ac.	210	15	0.276	T	+	
July 24-25	....	415	05	Ac.	170	20	0.249	T	+	5 gm. NaCl per os from this date on.
July 25-26	8.90	445	12	Amph.	195	23	3.160	T	+	
July 26-27	....	380	13	Amph.	185	29	4.710	T	+	
July 27-28	9.00	435	14	Amph.	187	25	3.603	1.75	+	8.5 mg. uranium nitrate, subcut. 1 p. m.
July 28-29	....	650	16	*	187	33	8.190	2.5	+	Vomitus frothy only.
July 29-30	7.60	850	17	*	065	123	11.390	*	+	Vomitus mixed with urine.
July 30-31	....	525	12	*	123	42	7.870	*	+	Dog refused food henceforth; 500 c.c. water offered. Vomited most at once. Amount retained (calculated) 100 c.c.
July 31-Aug. 1	7.23	200	06	*	086	19	11.100	*	+	Retained amount 125 c.c. 110 gm. creatinin injected intravenously. 5 p. m. 30 c.c. saline.
Aug. 1-2	....	160	13	Ac.	088	08	2.930	2.0	+	Retained 20 c.c. Fine tremor.
Aug. 2-3	6.90	67	13	Amph.	054	08	0.970	2.0	—	Retained 20 c.c. Fine tremor, apathetic and weak.
Aug. 3-4	....	37	17	Ac.	039	09	1.160	4.1	—	Retained 150 c.c. Fine tremor. Weaker, easily pushed over.
Aug. 4-5	6.66	67	20	Ac.	073	22	0.201	1.5	+	Retained 15 c.c. Fine tremor. Weaker, easily pushed over.
Aug. 5-6	....	50	18	Ac.	053	09	.....	0.4	—	Retained 10 c.c. Coarse tremor. Can scarcely stand. Nasal injection. Clonic spasm of fore paws on percussion over scapular muscles.
Aug. 6-7	Dog dead.									

* Vomitus admixed.

TABLE 3.—Acute and Subacute Nephritis. Creatinin Injections

Experiment 3.—Diet: water, 700 c.c.; meat, 15 gm.; cracker-meal, 125 gm.; lard, 50 gm.; bone ash, 13 gm.

Date	Weight, Kilos	Urine							Feces	Remarks
		Vol. c.c.	Sp. Gr. 10 xx	Reaction to Litmus	Creatinin, Mg.	Uric Acid Mg.	Chlorids, Gm.	Albumin, Gm.		
July 16-17	9.30	310	06	Ac.	166	11	0.155	T	+	
July 17-18	....	260	06	Ac.	152	10	0.156	T	—	
July 18-19	9.35	465	07	Ac.	279	20	0.372	T	+	
July 19-20	....	330	06	Ac.	198	11	0.198	T	+	
July 20-21	9.30	380	09	Ac.	151	14	0.228	..	—	
July 21-22	....	370	07	Ac.	232	15	0.222	T	+	
July 22-23	9.35	410	07	Ac.	258	17	0.164	T	+	
July 23-24	....	285	11	Ac.	169	18	0.215	1.0	+	8 mg. uranium nitrate subcuta. 12 noon.
July 24-25	9.25	515	12	Ac.	174	27	0.309	1.5	+	7 mg. uranium nitrate subcuta. 10 a. m.
July 25-26	....	190	13	Ac.	74	10	0.414	1.5	+	
July 26-27	8.85	325	06	Ac.	92	28	0.065	T	+	
July 27-28	....	150	..	Ac.	...	23	0.300	..	+	Urine lost in part.
July 28-29	9.30	445	09	Ac.	220	23	0.356	T	+	
July 29-30	....	450	10	Ac.	226	28	0.630	T	+	
July 30-31	9.15	390	10	Ac.	252	44	1.014	T	+	7.5 mg. uranium nitrate injected subcutaneously 5:50 p. m.
July 31-Aug. 1	....	410	10	Ac.	200	23	0.902	T	+	
Aug. 1-2	9.00	340	10	Ac.	158	19	0.816	T	+	
Aug. 2-3	....	420	10	Ac.	211	26	0.840	T	+	
Aug. 3-4	....	415	10	Ac.	212	27	0.747	0.5	+	20 mg. uranium nitrate injected subcutaneously 5 p. m.

Aug. 4-5	9.00	150	17	Alk.	99	18	0.075	1.75	+	Fecal mixture, no diarrhea.
Aug. 5-6	....	480	11	Ac.	193	58	0.192	0.5	+	
Aug. 6-7	8.90	355	15	Ac.	197	30	0.177	1.0	+	
Aug. 7-8	....	330	13	Ac.	187	45	0.231	1.0	+	
Aug. 8-9	8.95	335	14	Ac.	231	36	0.435	1.0	+	25 mg. uranium nitrate subcutaneously 4:30 p. m.
Aug. 9-10	....	400	13	Ac.	148	56	0.640	1.0	+	
Aug. 10-11	....	260	20	Ac.	152	49	0.416	1.0	+	
Aug. 11-12	9.00	230	20	Alk.	130	26	0.345	1.0	+	Fecal mixture, no diarrhea.
Aug. 12-13	....	305	13	Ac.	140	29	0.884	0.5	+	
Aug. 13-14	....	435	11	Ac.	241	26	1.174	0.5	+	91 mg. creatinin injected intravenously 5 p. m. 30 c.c. saline.
Aug. 14-15	8.95	325	12	Ac.	187	29	0.910	0.5	+	
Aug. 15-16	....	280	14	Ac.	153	25	0.840	1.0	+	
Aug. 16-17	....	260	12	Ac.	128	15	0.806	1.0	+	
Aug. 17-18	9.00	300	13	Ac.	156	23	0.750	1.0	+	
Aug. 18-19	....	225	14	Ac.	136	29	0.562	0.5	+	
Aug. 19-20	....	255	13	Alk.	96	22	0.612	0.75	+	Fecal mixture, no diarrhea.
Aug. 20-21	8.95	340	10	Ac.	122	27	0.544	0.5	+	
Aug. 21-22	....	415	11	Ac.	182	31	0.830	0.5	+	
Aug. 22-23	....	180	08	Ac.	100	19	0.396	0.5	+	70 mg. creatinin injected intravenously 4:31 p. m. 30 c.c. saline.
Aug. 23-24	8.95	330	10	Ac.	142	23	1.528	0.5	+	
Aug. 24-25	....	290	12	Ac.	77	26	0.464	0.5	+	
Aug. 25-26	....	230	10	Ac.	99	20	0.506	0.5	+	

TABLE 4.—Acute Nephritis and Creatinin Injection

Experiment 4.—Diet: water, 700 c.c.; meat, 15 gm.; cracker-meal, 125 gm.; lard 50 gm.; bone ash, 15 gm.

Date	Weight, Kilos	Urine							Feces	Remarks
....	....	Vol. c.c.	Reaction to Litmus	Sp. Gr. 10 xx	Creatinin, Mg.	Chlorids, Gm.	Uric Acid, Mg.	Albumin, Gm.	...	
Aug. 8-9	14.0	480	Amph.	12	284	1.594	28	T	+	
Aug. 9-10	.....	470	Amph.	07	272	1.598	32	T	+	
Aug. 10-11	.....	450	Amph.	08	185	1.495	27	T	+	
Aug. 11-12	14.0	525	Amph.	08	291	1.365	31	T	+	
Aug. 12-13	.....	130	Ac.	20	172	1.300	43	0.5	+	30 mg. uranium nitrate injected subcutaneously 11:30 a. m.
Aug. 13-14	.....	600	Ac.	16	302	2.040	34	2.5	+	
Aug. 14-15	13.10	650	Alk.	20	280	0.390	56	4.5	+	Vomitus mixed with urine.
Aug. 15-16	.....	380	Alk.	21	170	0.532	34	5.0	+	Vomitus mixed with urine.
Aug. 16-17	.....	285	Ac.	18	90	0.342	17	2.0	+	Vomitus mixed with urine.
Aug. 17-18	13.30	400	Ac.	10	83	0.960	36	1.0	+	Vomitus mixed with urine. 0.1835 gm. creatinin injected intravenously 5 p. m. 30 c.c. saline.
Aug. 18-19	.....	160	Ac.	10	50	0.736	09	1.0	+	Vomitus mixed with urine.
Aug. 19-20	.....	70	Ac.	07	11	0.196	17	0	+	Vomitus mixed with urine.
Aug. 20-21	14.10	212	Ac.	10	36	0.805	14	0	+	Vomitus mixed with urine.
Aug. 21-22	.....	315	Ac.	07	94	0.882	19	0	+	Vomitus mixed with urine.
Aug. 22-23	.....	545	Ac.	06	117	1.417	34	0	+	
Aug. 23-24	13.20	850	Ac.	08	161	1.700	37	0	+	Vomitus mixed with urine.
Aug. 24-25	.....	840	Ac.	08	184	2.688	44	0	+	
Aug. 25-26	.....	270	Ac.	09	202	.....	..	0	+	

The figures in the accompanying table (Table 5) indicate that polyuria was obtained in all cases. As to anuria, this was not clearly observed in any case, due to the necessity of proceeding promptly with further injections.

TABLE 5.—POLYURIA

	Vol in c.c.			
Experiment	1	2	3	4
Average normal	266	425	360	431
Maximum normal	345	460	465	525
Uranium nitrate nephritis	331	435	285	130
	681	650	515	600
	420	850	190	650*
	...	525	325	...

* Vomitus admixed.

D. Chlorids.—The excretion of chlorids has been carefully investigated by Schlayer and his associates as well as by Austin and Eisenbrey.[21] These authors found a decrease in the excretion of chlorids. Mosenthal[22] has found that the excretion of chlorids may be increased, normal in amount or diminished at times, according to the conduction of the experimental nephritis. It has also been stated by Pohl,[15] and Austin and Eisenbrey that there is an initial increase coincident with the polyuria, after which the excretion of chlorids decreases. This was found to be the case in Experiment 4. The results of the other experiments are inconclusive.

E. Uric Acid.—The question of uric acid excretion in uranium nephritis, acute or subacute, does not seem to have attracted the attention of investigators up to now, for no references have been found in the literature. Table 6 presents some results in this connection.

From the data in this table (Table 6) we may conclude that uranium nitrate nephritis causes an increase in the amount of endogenous uric acid in the urine; that in the subacute form the excretion remains high.

F. Creatinin.—It appears that the elimination of creatinin in acute uranium nephritis has not been studied. It is, however, interesting to note that in potassium chromate nephritis—a tubular form—Levene and Kristeller,[23] and Lefmann[4] found a decrease in the excretion of creatinin. J. L. Green[24] notes that "creatinin was slightly reduced," but his results are by no means conclusive. Table 7 shows the results for acute uranium nephritis.

In subacute nephritis the amount of creatinin excreted is reduced. The protocol of Experiment 3 shows that after four doses of uranium had been given over a period of twenty-one days, the succeeding seven

21. Austin and Eisenbrey: Jour. Exper. Med., 1911, xiv, 366.
22. Mosenthal: Personal communication.
23. Levene and Kristeller: Am. Jour. Physiol., 1909, xxiv, 45.
24. Green, J. L.: Jour. Pathol. and Bacteriol., 1909, xiii, 296.

days showed an average excretion of 129 mg., and the days thereafter 108 mg. The normal, as may be seen in Table 7, was 205 mg.

TABLE 6.—Uric Acid Excretion

Experiment 2.	Mg.		
Normal average	21		
Nephritis	25	Uranium nitrate,	
	33	8.5 mg. subcutaneously.	
	123		
	42		
Experiment 3.	Mg.		Mg.
Normal average	14		56
Nephritis	18	Uranium nitrate, 8 mg.	49
	27	Uranium nitrate, 7 mg.	26
	10	subcutaneously.	29
	28		26
	23		29
	23		25
	28		15
Nephritis	44	Uranium nitrate, 7.5 gm.	23
	23	subcutaneously.	29
	19		22
	26		27
Nephritis	27	Uranium nitrate, 20 mg.	31
	18	subcutaneously.	19
	58		23
	30		26
	45		20
Nephritis	36	Uranium nitrate, 25 mg. subcutaneously.	
Experiment 4.	Mg.		
Normal average	29		
Nephritis	43		
	34	Uranium nitrate, 30 mg.	
	56	subcutaneously.	
	34		
	17		

Intravenous Creatinin Injections.—No record of excretion after intravenous injections of creatinin has been found. There are, however, several observations on its excretion when fed or subcutaneously injected. Folin[25] found that if creatinin were ingested by a normal patient, 75 per cent. was excreted. Wolf and Shaffer[26] found that 80 per cent. of ingested creatinin was excreted. Voegtlin and Towles[27] found that when creatinin was ingested, 36.3 per cent. and 62.5 per cent. (two experiments) were excreted in twenty-four hours, while if injected subcutaneously, 54.5 per cent. and 72.7 per cent. (two experiments) were excreted.[28] Mellanby,[29] Lefmann,[4] and Klercker[3] state that ingested

25. Folin, O.: Am. Jour. Physiol., 1905, xiii, 66.
26. Wolf and Shaffer: Jour. Biol. Chem., 1908, iv, 439.
27. Voegtlin and Towles: Jour. Biol. Chem., 1912, x, 479.
28. Calculated from protocols.
29. Mellanby, E.: Jour. Physiol., 1907-08, xxxv, 447.
30. v. Hoogenhuyze and Verploegh: Ztschr. f. physiol. Chem., 1905, xlvi, 415.

creatinin is excreted in great part. Van Hoogenhuyze and Verploegh[30] state that 100 per cent. of injected creatinin is excreted. The data in Table 8 lead us to the conclusion that when intravenously injected, creatinin is excreted "in toto." From the protocols it will be seen that this did not take more than forty hours.

TABLE 7.—CREATININ EXCRETION IN ACUTE URANIUM NEPHRITIS

Experiment	1	2	3	4
	Mg.	Mg.	Mg.	Mg.
Normal average	210	190	205	258
Uranium nitrate nephritis	281*	187*	169*	172*
	228	187	174	302
	114	65	74	280
		123	92	170
				90

* Uranium nitrate subcutaneously. Exp. 1, 10 mg.; Exp. 2, 8.5 mg.; Exp. 3, 15 mg.; Exp. 4, 30 mg.

G. Creatinin Injections During Uranium Nephritis.—No record of creatinin injections in dogs or other animals having uranium or other experimental nephritides has been found. In view of the results, this phase of the subject deserves careful consideration.

TABLE 8.—EXCRETION OF CREATININ

Experiment	1	1	1	1	3	3
	Mg.	Mg.	Mg.	Mg.	Mg.	Mg.
Normal (average)	210	210	210	210	165*	127*
Average 3-day period following injection	330	245	223	267	193	141
Average 3-day period with injected amount subtracted	280	209	190	234	163	114

* Excreted during chronic nephritis.

When a dog with uranium nephritis was injected with an amount of creatinin equivalent approximately to one-half the normal excretion, the animal either died (two cases) or showed a remarkable decrease in renal activity (one case). The data show (Tables 9 and 10) that not only was the injected creatinin not excreted, but the excretion lay far below either the normal or the amount excreted in the previous nephritic period.

TABLE 9.—CREATININ EXCRETION AFTER INJECTION OF APPROXIMATELY ONE-HALF THE USUAL EXCRETION DURING NEPHRITIS

	Experiment 2		
	Volume, c.c.	Creatinin, Mg.	Uric Acid, Mg.
Average normal	425	190	21
Average after nephritis	615	140	55
Average after creatinin injection	96	65	13

The excretion of the other substances subjected to study shows a noteworthy state of affairs, namely, a great decrease in the excretion of water, chlorids and uric acid; in other words, there was an apparent

arrest of renal function, followed in two instances by death and in one by recovery. This last case (Table 11) deserves further attention, since an examination of the figures shows that after a certain period (three days) the kidney began to excrete more readily, and that the substances increased daily in amount until the creatinin had reached the normal amount, and until uric acid, chlorids and water had far exceeded it; in other words, what appeared to be a physiological compensation took place.

TABLE 10.—CREATININ EXCRETION AFTER INJECTION OF APPROXIMATELY ONE-HALF THE USUAL EXCRETION DURING NEPHRITIS

	Experiment 1	
	Creatinin, Mg.	Volume, c.c.
Average normal	210	266
Average nephritis	207	477
Average creatinin injection	3	127

The following is a description of the animals' condition after creatinin was injected. Dogs 1 and 3 will be described together, as they showed practically the same symptoms and in the same order. These dogs one day after the creatinin injection became apathetic. They did not jump about their cages when approached as had previously been the case. Two days later a fine muscular tremor was noted. The dogs lay quietly in their cages. If placed on their feet they were easily bowled over by a

TABLE 11.—APPARENT PHYSIOLOGICAL COMPENSATION IN CREATININ EXCRETION AFTER INJECTION OF EXCESS DURING NEPHRITIS

Experiment 4.

	Volume, Cc.	Creatinin, Mg.	Uric Acid, Mg.	Chlorids, Gm.
Average (normal)	431	258	29	1.513
Average (nephritis)	403	231	41	1.065
Creatinin injection	400	83	36	0.960
	160	50	9	0.736
	70	11	17	0.196
	212	36	14	0.805
	315	94	19	0.882
	545	117	34	1.417
	850	161	37	1.700
	840	184	44	2.688
	270	202	..	.....

gentle push and did not jump up again. The following day a coarse tremor was noted which was spasmodic only. The respiration was labored, perhaps due in part to a nasal infection of a purulent nature.[31] The eyes also now showed a purulent discharge. Neither of these inflam-

31. The fact that this infection occurred but one day before death, and after the renal reaction to the creatinin injection had commenced, warrants the belief that it was in no way responsible for the animal's death, and was only a manifestation of lowered resistance due to the toxic influence on the animal as shown by his changed actions and urinary excretions.

matory changes had been present before. In Dog 3, percussion near the scapular spine gave a very active reflex contraction of the fore leg, which on two occasions developed into a clonus. The dogs became more and more apathetic, lying quietly in their cages, not reacting to calls and unable to stand when placed on their feet. This lasted until they died. If at any time after the creatinin injection water was placed in the cages the dogs drank, but vomited at once. Dog 4 showed no symptoms whatsoever and throughout the experiment appeared normal.

But before offering any explanation of these phenomena, the results of creatinin injections in a subacute uranium nephritis must be noted. Here, as the figures in Table 12 show, the secretion of neither creatinin, uric acid, chlorids nor water was affected. It is on this finding that a possible explanation of the phenomenon in the acute nephritis may be

TABLE 12.—Results of Injection of Creatinin During Subacute Uranium Nephritis

Experiment 3.

	Vol., c.c. ..	Creatinin, Mg.	Uric Acid, Mg.	Chlorids, Gm.	Remarks
Average normal	360	205	14	0.213	
After four uranium injections during 21 days	435	241	26	1.174*	Injected 91 mg. creatinin.
	325	187	29	0.910	
	280	153	25	0.840	
	260	128	15	0.806	
	300	156	23	0.750	
	225	136	29	0.562	
	255	96	22	0.612	
	340	122	27	0.544	
	415	182	31	0.830*	Injected 70 mg. creatinin.
	180	100	19	0.396	
	330	142	23	0.528	
	290	77	26	0.464	
	230	99	20	0.506	

* Raised chlorid excretion due to saline injection fluid.

based. In the acute nephritis, the tubules are all more or less severely injured. If to the normal burden (which, as the figures show, is poorly borne so far as creatinin goes), we add the additional burden of excreting more creatinin, we can readily imagine that the injured cells, now taxed far beyond their powers, would fail to act as well as before, and a more or less complete arrest of renal function would result. In subacute nephritis, cellular regeneration or atrophy takes place, so that the kidney probably contains sufficient normal tubular epithelium to take care of a certain amount of creatinin beyond that presented to the kidney by body metabolism, and thus no ill effects occur. What this amount is, and whether it approaches the normal, has not been demonstrated up to now.

The whole matter seems, moreover, to have another interesting side when we consider that creatinin is increased in fever in general

(Leathes[32]), and specifically in acute fevers, e. g., pneumonia (Wolf and Lambert[33]) and typhoid fever (Shaffer,[34] and Ewing and Wolf[35]); and when we consider that the diphtheria, cholera and colon bacilli, as well as the pneumococcus, cause a tubular nephritis (Aschoff[36]).

The manner of production of a kidney condition which would give rise to uremia in certain febrile diseases might be explained as follows: Taking creatinin as an example of a normal urinary substance excreted by the tubules of the kidney, and reviewing briefly what occurred in Experiments 1, 2, 3, and 4, we may conclude that animals with a tubular nephritis and given a hypercreatininemia, showed an arrest of renal function followed in two instances by death. When the hypercreatininemia was omitted, there was no death from nephritis of similar intensity.[37] In other words, hypercreatininemia taxed the kidney beyond its power of function and the margin of safety or limit of function was overstepped.

Let us now suppose the existence of a febrile condition, in which the excretion of creatinin is raised; the tubules would then be taxed beyond the usual. Add to this a tubular nephritis and we have the reverse of what took place in the experiment; that is, instead of tubular nephritis followed by hypercreatininemia we have hypercreatininemia followed by tubular nephritis, both of which would naturally entail similar results, so far as effects on the tubule are concerned.

As stated above, creatinin is taken only as an example of a urinary substance normally excreted by the kidney tubule. There seems no reason to believe that other normal substances which are increased in fever and excreted by the tubules would not act in a similar way; that is, to overtax an already overfunctioning kidney whose condition had been aggravated by a tubular nephritis.

In brief, it would seem probable that the factors which reduced the total functioning powers of the kidney in the above experiments have been a tubular nephritis followed by a further taxing of the tubules by the presentation of excessive amounts of a substance normally excreted by them; and that the same factors, even though reversed in order of occurrence, might act in the same way in human febrile diseases complicated by tubular nephritides.

What may cause the uremia, normal or abnormal substances, is not known. We have only been concerned here with the mechanism of the retention of these substances.

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32. Leathes, J. B.: Jour. Physiol., 1909, xxxv, 205.
33. Wolf and Lambert: THE ARCHIVES INT. MED., 1910, v, 406.
34. Shaffer: Am. Jour. Physiol., 1908, xxiii, 1.
35. Ewing and Wolf: THE ARCHIVES INT. MED., 1909, iv, 330.
36. Aschoff: Pathologische Anatomie, 1911, ii, 450.
37. This has been shown by many of those quoted above who have worked with uranium.

CONCLUSIONS

1. In acute uranium nitrate nephritis, (1) creatinin is excreted in decreased amounts, and (2) uric acid is excreted in increased amounts (Experiments 2, 3, 4).

2. In subacute uranium nitrate nephritis, (1) creatinin is excreted in decreased amounts (two weeks), but (2) uric acid and (3) chlorids are excreted in increased amounts (two weeks) (Experiment 3).

3. Creatinin injected in normal dogs is excreted "in toto" (Experiment 1).

4. Creatinin injected in acute uranium nephritis causes (1) endogenous and (2) injected creatinin (Experiments 1, 2, 4), (3) uric acid, (4) chlorids and (5) water, to be excreted in decreased amounts (Experiments 2, 4); (6) death may ensue.

5. Creatinin injected in subacute uranium nephritis (Experiment 3) is excreted "in toto," and apparently does not affect the excretion of endogenous creatinin, uric acid, chlorids or water since these are unchanged.

I wish to express my thanks to Dr. Wm. J. Gies for the valuable assistance I have received while carrying out this work.

437 West Fifty-Ninth Street.

A CASE OF AURICULAR FIBRILLATION WITH A POST MORTEM EXAMINATION *

ALFRED E. COHN, M.D., AND JAMES D. HEARD, M.D.
PITTSBURGH

CASE REPORT

History.—The patient, Mrs. T. G., was 37 years old. Her weight was 55 kilos. She was first admitted to St. Francis Hospital, Pittsburgh, Jan. 17, 1912; her chief complaint being shortness of breath. Dyspnea had been present during the past four to six weeks, during which period she had also experienced palpitation and precordial pain; occasional night sweats had occurred during the past few months, together with frequent "colds," during the course of which the patient would bring up blood-stained sputum. Her past medical history was as follows: She had chorea during childhood, rheumatic fever in 1908 and again in 1911, measles, diphtheria and small-pox in early life. She was not subject to sore throat. The patient had given birth to three healthy children and had had no miscarriages. She had worked hard. Her habits were good.

Examination.—The physical findings on the day following admission were, in brief, as follows: The patient was a slender, middle-aged woman, lying in bed without any apparent pain or discomfort. Her temperature was 98.4 F., pulse-rate 120 to 130, respiration 22 to 24, systolic blood-pressure 120. She coughed occasionally. There was slight cyanosis, but no jaundice nor edema. Her eyes, mouth and tonsils were negative. The external jugular veins were pulsating. The thyroid gland was not enlarged. The thorax was barrel-shaped and allowed only shallow respiratory excursions; there was a pronounced Harrison's furrow. Expiration was prolonged over the upper lobes of both lungs. Numerous moist râles were heard over the entire posterior aspect of the left lung and in the left lower axillary region. There was pronounced precordial bulging and diffuse heaving synchronous with the heart beat, the point of maximum intensity being in the sixth interspace slightly to the right of the left anterior axillary line. The cardiac impulse was marked and sudden and was preceded by a rough vibratory presystolic thrill. The right cardiac border was 5 cm. to the right of the mid-sternal line, and the left border 12 cm. to the left, at the third interspace. A presystolic rumble terminat-

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* From the Hospital of the Rockefeller Institute for Medical Research, New York.

ing in a sharp flapping first sound was heard at the apex and was followed by a short puffing murmur, heard over a wide area including the left axilla. The second sound at the pulmonic area was markedly accentuated and louder than that at the aortic area. The rhythm was regular. The abdomen showed marked epigastric pulsation. The blood, urine and feces showed no abnormalities.

Treatment.—The patient's condition remained unchanged for five days, during which period the pulse-rate averaged 120, the rhythm being always regular and the heart sounds continuing as noted at the first examination. It is not known whether digitalis had been administered before her admission, but on Jan. 22, 1912, the tincture of digitalis was first prescribed in the hospital, the dose being 1 dram a day. After the administration of one-half dram, the patient was awakened by severe palpitation. The resident physician noted at this time that the apex rate had fallen to 80 and that the pulse was grossly irregular in rhythm and in force. The patient was not seen by the physician in

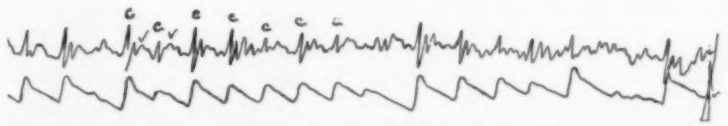

Fig. 1.—The upper line shows the time in 0.2 seconds. The second and third lines are curves of the jugular (venous) and radial pulses. Complete irregularity of the heart (auricular fibrillation) is present.

charge until 2 drams of the tincture of digitalis had been administered. The medication was then discontinued. It was noted at this time that the presystolic murmur and thrill had disappeared. In a polygraphic tracing taken January 24, the radial curve showed a *pulsus irregularis perpetuus;* and the venous, the ventricular type.

All subsequent tracings were of the same character, so that the conclusion was reached that auricular fibrillation was present. The slower rate of the ventricles continued until the patient was discharged from the hospital, Feb. 7, 1912. The change to a slower rate and an irregular rhythm coincided with rapid improvement in the general condition, and also in regard to dyspnea, cough and cyanosis. When the patient left the hospital, the circulation was restored to a condition of compensation.

Second Admission.—On her second admission, March 12, 1912, the patient was brought to the hospital in a condition of orthopnea. The temperature was 102.6 F.; the cardiac rhythm was completely irregular, the apex rate being 110; the respirations were 54 per minute. There was almost constant coughing with expectoration of much thin frothy

fluid which did not contain blood. There was marked general subcutaneous edema. Auscultation of the chest disclosed the presence of numerous fine and coarse râles which could be heard over the entire posterior aspect; resonance was impaired at both bases. The abdomen was dome-shaped and flat on percussion in both flanks. The liver was pulsating and its lower border extended 7 to 8 cm. below the costal margin at the mid-clavicular line. The urine contained albumin and hyaline and granular casts. Next morning at 9:30, after having passed a fairly comfortable night, the patient was in no distress. One hour

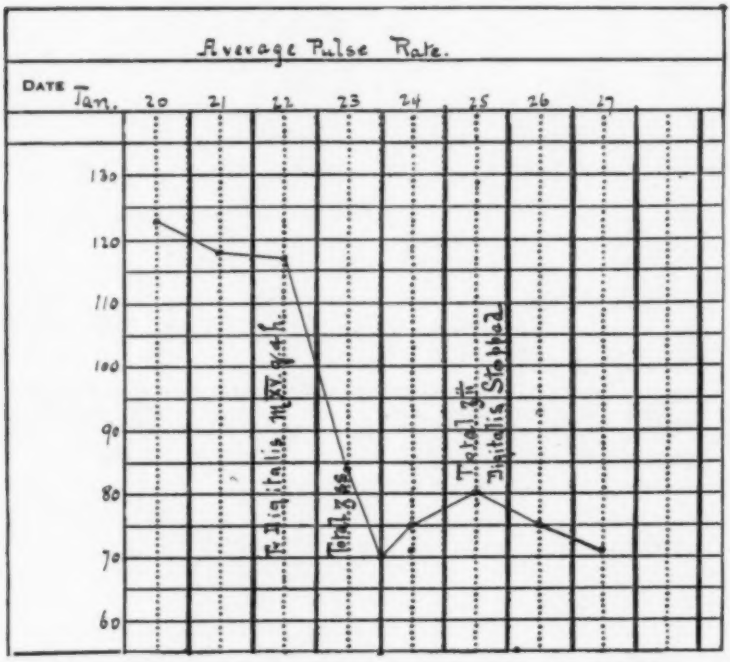

Fig. 2.—Chart showing average pulse-rate as affected by digitalis.

later she suddenly developed delirium cordis, with urgent dyspnea and general cyanosis. At this time Dr. H. G. Schleiter saw the patient with one of us in consultation, and it was decided to administer strophanthin intravenously, and to follow this by 1 dram of the tincture of digitalis daily by mouth. The injection was subsequently carried out by Dr. Schleiter, who has kindly furnished the following note and the accompanying tracing:

"March 13, 1912. At 11:20 a. m., the patient was in extreme distress, sitting up against pillows and panting for breath. The following con-

ditions were noted: The lower extremities were extensively edematous. The right border of the heart was 2 inches to the right of the mid-line; the left border was 4 inches to the left in the third interspace; the apex, 5 inches to the left in the sixth interspace. The pulse-rate, taken at the apex, was 164 per minute and showed complete arhythmia. Jugular tracings were not obtainable, but the radial pulse showed beats varying constantly in time and force, with no underlying dominant rhythm demonstrable; it does not appear reasonable to doubt that auricular fibrillation was present. Fluid was present at the bases of both pleural cavities. Many crepitant râles were heard. There was ascites; the liver

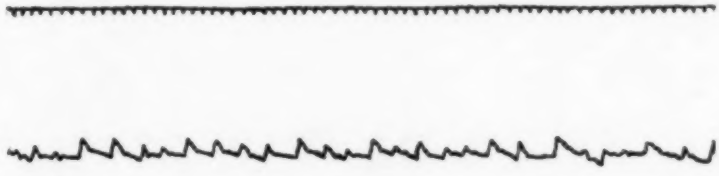

Fig. 3

Fig. 3.—A curve of the radial artery before the administration of strophanthin, 0.5 mgm., intravenously.

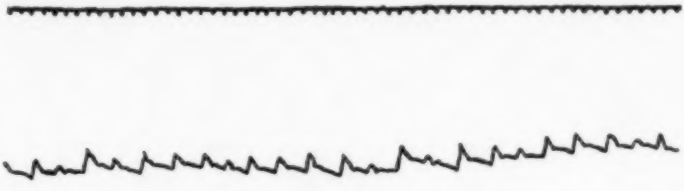

Fig. 4.

Fig. 4.—The same thirty minutes after the intravenous injection.

pulsated and the edge was felt at the level of the umbilicus. The patient was given an intravenous injection of 0.5 milligrams strophanthin. Within five minutes she appeared less ill, and in twenty minutes she was breathing quietly as if after a hypodermatic injection of morphin; the pulse, still showing fibrillation, had fallen to a rate of 116 per minute. A second injection of strophanthin (0.5 milligrams) was given at 3:30 p. m. It is of interest to note that after 7 drams of the tincture of digitalis had been administered, the pulse-rate had fallen to 84 per minute and the patient's condition had greatly improved. The heart

outline had not been reduced, the characteristic irregularity was still present, and the liver border still remained at the level of the umbilicus, where it had been on admission to the hospital."

On the day following and for several days subsequent to the injection of strophanthin, considerable pain and swelling were present in the arm which had been chosen for its administration. Urgent subjective symptoms did not return. During the first three days after the beginning of

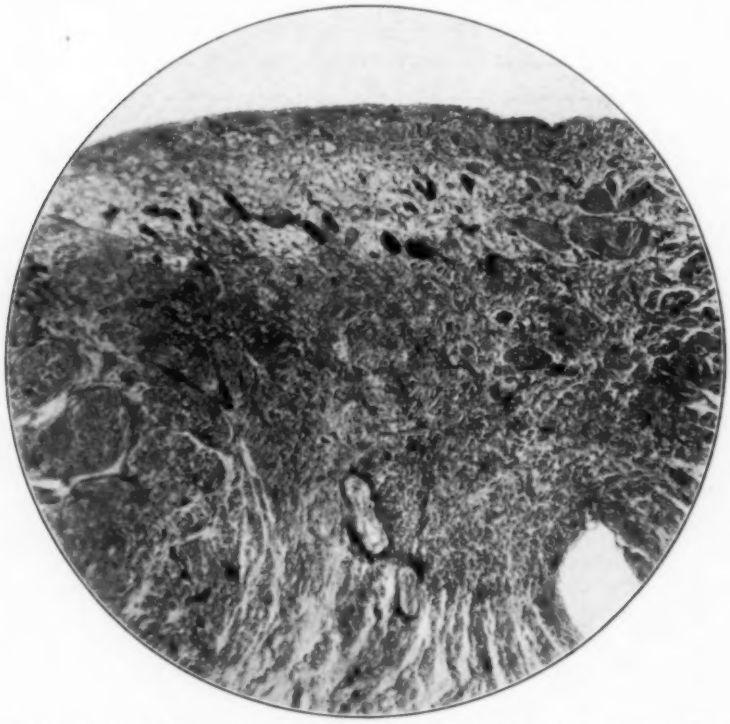

Fig. 5.—Microphotograph of the sino-auricular node. Slide 257. The pericardium is directed upward. The new-formed, thin-walled blood-vessels are seen in the subpericardial fat. The node has a triangular shape, base toward the pericardium.

the administration of digitalis, the rate of the heart occasionally reached 120 to 135, but subsequently it fell to normal and remained so after the withdrawal of the drug. Improvement was progressive. On March 24 the urine was free from albumin and casts. The patient was discharged in April, 1912, with the circulation fairly well maintained.

Third Admission.—About five weeks later, on May 21, 1912, the patient was admitted for a third time. She said that she had been very

comfortable since leaving the hospital, spending most of her time in her chair. She had taken no medicine. The evening before admission she began to be short of breath, the dyspnea soon becoming very urgent. On admission, the patient was found to be in a condition of marked decompensation. She had orthopnea, cyanosis, general edema, anasarca and albuminuria. The temperature was normal; the respirations 40; the rate of the heart at the apex 160; the radial pulse was weak and inter-

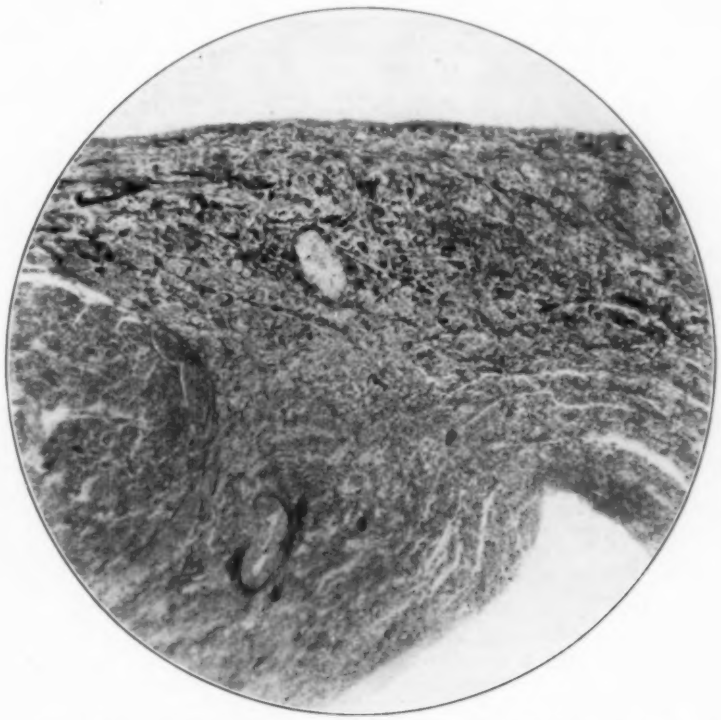

Fig. 6.—Microphotograph of the sino-auricular node. Slide 309. The node has an elongated form, its long axis parallel to the pericardium. A normal relation between muscle and connective tissue is seen.

mittent, the average rate being about 100; the area of cardiac dulness was like that on the previous admission; the lower border of the liver was at the level of the umbilicus. There was constant coughing and expectoration of much white frothy fluid. The patient was given the tincture of digitalis. She had four hours sleep after two injections of one-fourth grain of morphin sulphate. She suffered less discomfort next morning, but in the evening had marked dyspnea, tossed about in bed and refused, at

times, to answer questions. Strophanthin (1 milligram) was administered intravenously by the resident physician, but some of the solution escaped into the tissues so that it was not possible to determine the exact quantity which was absorbed. The patient gradually became more comfortable, but no striking change in her condition was noticed. May 23, 1912, the patient was very cyanosed and moved continually in bed. She was stuporous, but responded to questions. Her temperature was normal; the heart rate at the apex was 120, and the radial pulse 80. After a vein had been exposed by dissection, strophanthin (1 milligram) was injected into it, but without apparent result on the heart rate or mass movement of blood. Two days later, May 25, 1912, the temperature suddenly rose to 105.4 F., without a premonitory chill. The patient was very restless. There was marked icterus. The leukocytes numbered 15,000, and in the differential count there were 95.6 per cent. polynuclear cells. Twelve ounces of blood were withdrawn by venesection. During May 26, 1912, the temperature again reached 105.4 F. The patient was very restless and cyanotic. On the next day there was progressive failure of the circulation. The cardiac impulse was tapping in character, and the rhythm was grossly irregular. Pulmonary edema set in. The temperature ranged between 101 and 106 F. Death occurred May 28, at 2:30 a. m. Blood-culture showed the presence of an unidentified streptococcus.

An autopsy was performed several hours later by Dr. Oskar Klotz, to whom we are indebted for the report of the post mortem examination.

NECROPSY

The body was that of a slightly built woman of about middle age. The nutrition was fair. The pupils were both dilated, the left being larger than the right. The breasts were small and atrophied. There was some excoriation of the skin over the sacrum. The external orifices were without change. The skin tissue everywhere showed a marked yellow pigmentation, as did also the sclera.

Neck Organs: The trachea was a little congested but did not contain excessive exudate. The lymph-nodes at the bifurcation of the trachea showed a single small calcareous nodule the size of a mustard seed. The esophagus showed no change. The thyroid was not enlarged but was rather meaty looking. The tissue of the neck below the thyroid gland appeared edematous, and in it were several dark red lymph-nodes.

Thorax: There were some old adhesions along the posterior border of each lung. The apex on each side was free. There was no excess fluid in either pleural cavity. The pericardium contained about 75 c.c. of a clear yellow fluid.

Left Lung: The organ crepitated throughout. The tissues appeared a little heavy, but there was no evidence of edema. There was only a slight marbling of black pigment. On section the lung substance was a little congested. The arteries of the lung showed some irregular thickening of their walls. The hilus nodes were not enlarged. The bronchi appeared quite clear.

Right Lung: The organ was very similar to that on the left side. There was some slight congestion but no edema. In one of the main pulmonary arteries there was a flat area showing adherent grayish red clot. This clot did not obstruct the artery. The hilus nodes were without change.

Heart: See below.

Aorta: The aorta showed some diffuse thickening of the intima in the arch and in the descending thoracic portion. The carotid arteries showed some irregular nodular areas near the bifurcation.

Abdomen: On opening the abdomen the partially distended small intestine protruded. The great omentum showed an adhesion to the right of the broad ligament. The spleen was connected by old adhesions to the diaphragm. There were some old bands of fibrous tissue between the left lobe of the liver and the diaphragm. The left ovary had some adhesions to the sigmoid. There was no excess fluid in the peritoneal cavity.

Alimentary Canal: The stomach and intestines showed nothing unusual. There was some congestion of the lower portion of the small and large intestines. The mesenteric lymph-nodes were not enlarged.

Liver: The organ was rather swollen and was flabby. The outer surface of the left lobe showed some old adhesions. The organ was quite pale in color. The gall-bladder contained thick brown bile, which contained many pigmented granules. The liver on section was bright yellow, in which some dark red spots and streaks could be distinguished. The lobules were not distinctly marked. There was no evidence of fibrosis. The yellow areas were not definitely depressed but some resembled areas of necrosis.

Spleen: The spleen was tense and firm. On section the organ appeared dark and firm in certain areas, while in others the tissue was soft and could be readily scraped with a knife. The softer areas appeared more particularly in the center of the organ. The Malpighian bodies were indistinct.

Kidneys: Both organs were very much alike. In each instance the capsule was quite thin and not adherent. The cortex was gray and somewhat swollen; it was poorly defined from the medulla. The pelvis and ureters were normal.

Adrenals: Both adrenals were quite large. The cortex was red and showed no evidence of fat. The medulla was not enlarged and was of a gray color.

Bladder: The organ was of good size. The walls were thin and pale.

Genitalia: The tubes were both normal. The ovary in the left side contained a cyst 2.5 cm. in length. The uterus was normal in size and appearance. The cervix showed the presence of two old tears. In the vagina there was some excoriation of the epithelium on the posterior wall just below the cervix.

MICROSCOPICAL REPORT

Lymph-Nodes: The lymph sinuses throughout were much dilated, as were also the blood-vessels. The sinuses were filled with lymphocytes, a few polymorphonuclear leukocytes and occasional endothelial cells. There was much carbon pigment.

Lung: The alveoli were of usual size. Their walls were thin and there was no evidence of any inflammatory exudate into the alveoli.

Heart: Sections of the heart muscle showed a rather poorly staining tissue in which the muscle fibers did not stain evenly. The muscle fibers appeared rather narrow. The striations of the muscle fibers were indistinct and these were seen in broken fragments in the neighborhood of some of the blood-vessels. About these blood-vessels was an excess amount of connective tissue. In other places the capillaries lying between the muscle bundles were distended with blood with occasional extravasation of red blood-cells into the surrounding tissue. Here and there a number of polymorphonuclear leukocytes were seen in the interstitial tissue. Portions of the heart muscle cut on the freezing microtome showed an abundance of fat deposited within the muscle cells. This fatty degeneration was irregularly distributed through the tissue; in places it was very marked. Islands of connective tissue were also evident in the vicinity of the blood-vessels.

Thyroid: Sections of the thyroid gland showed tissue with many medium sized alveoli containing colloid material. The alveolar walls were quite thin and the epithelium somewhat flattened.

Kidney: In the cortex of the organ the glomeruli were of good size and they commonly showed fairly wide capsular spaces. The tubules of the cortex were large, many of them had wide lumina and contained some debris. The cells lining the tubules were of irregular size and stained poorly.

Liver: The structure of the organ was much altered. The central zones of the lobules were almost entirely destroyed, there being no liver columns in these regions. The sinuses were much dilated and there appeared to be an extravasation of red blood cells into the surrounding tissues. Each lobule showed only a rim of liver cells in the periphery.

Spleen: The organ was intensely congested so that the normal markings were almost obliterated. The Malpighian bodies were small.

BACTERIOLOGICAL REPORT

Blood taken a day before death contained streptococci. The biologic character of this organism was not identified.

Pathologic and Bacteriologic Diagnosis: (Rheumatism); chronic sclerotic mitral endocarditis; stenosis of mitral valve; chronic interstitial myocarditis; chronic sclerotic aortic endocarditis (slight); dilatation of heart (left ventricle and right auricle); hypertrophy of heart (left ventricle); milk spots of heart; fatty degeneration of heart; acute interstitial myocarditis; hydropericardium; thrombosis of pulmonary artery; sclerosis of pulmonary artery; old bilateral pleural adhesions; obsolete tuberculosis of peribronchial glands; chronic congestion of lung; peritoneal adhesions; chronic perisplenitis; cardiac spleen with acute splenitis; chronic perihepatitis; nutmeg liver; bile sand; central necrosis of liver; hemorrhage into liver; cloudy swelling of kidney; enlarged adrenals; cyst of ovary; chronic perisalpingitis; old laceration of cervix; decubitus ulcer of sacrum and vagina; septicemia (streptococcus).

TECHNIC OF EXAMINATION OF HEART

Heart: The heart was fixed in Zenker's solution. The area containing the sino-auricular node was washed and hardened in alcohol. The rest of the heart was taken out of Zenker's solution, washed in running water and then sent for examination in a 1 per cent. formaldehyd solution. It was then washed and preserved in alcohol. The length of the heart in the fixed state was 12 cm. from the auriculo-ventricular groove to the apex on the anterior surface, and 9 cm. on the posterior surface. There was a moderate amount of subpericardial fat along the right border of the heart; here there was a milk spot measuring 4 by 2.5 cm. A similar one measuring 1.5 by 1.5 cm. was found near the apex on the anterior surface of the right ventricle. The cavity of the right auricle was dilated but not hypertrophied. The endocardium was white and somewhat yellowish. A small Chiari net guarded the opening of the coronary sinus. The tricuspid valve admitted three fingers; the borders of the flaps were thickened. The right ventricle was neither dilated nor hypertrophied. The pulmonary valve was normal. The cavity of the left auricle was much dilated. The endocardium was thick and white. There were no vegetations. The mitral valve admitted two fingers. The edges of the flaps were much thickened and were rolled in on the auricular surface. The cavity of the left ventricle was slightly dilated but not hypertrophied. The wall measured 15 mm. at the base, 17 mm. at the level of the papillary muscles and 8 mm. at the apex. The outflow tract of the ventricle was more dilated than the left half of the cavity, and the endocardium lining it was white. The chordae tendineae were shorter and slightly thicker than normal. There were two small false posterior moderator bands. The corpora Arantii of the cusps of the aortic valve were thickened. The cusps themselves were adherent to each other at their points of intersection; otherwise they were normal. The coronary arteries were normal. The heart presented no congenital anomalies.

Sino-Auricular Node: The area at the cavo-auricular junction containing the sino-auricular node was hardened, embedded, cut and stained in the manner

employed and described elsewhere.[2] The sections were cut at a thickness of 12 microns at right angles to the long axis, and every fifth section was mounted. On account of the fixation in Zenker's solution, bichlorid precipitation occurred but was removed successfully by immersing the sections in Lugol's solution for one week before staining. The number of sections cut was 2,235, so that the length of the node after embedding was 26.82 mm.[3] The relation of the upper extremity of the node to the cavo-auricular junction could not be ascertained because the tissues had been excised from the heart before it was sent for examination, and the normal morphologic landmarks were consequently destroyed. The shape and dimensions of the transverse section of the node varied at different levels. In its upper extremity it was circular and its diameter was 1 mm. It lay directly under the pericardium, the wall of the auricle measuring 3.5 mm. There was a small hemorrhage close to the node. In the subpericardial fatty and connective tissue and also sometimes encroaching on the substance of the node itself, but confined almost wholly to the nodal area, there were many thin-walled blood-vessels, probably inflammatory or degenerative in origin. All of these, as well as the other vessels seen in this series, showed very marked congestion. A short distance below its upper extremity, the node lay 2 mm. deep from the pericardium and precisely at the junction of the taenia terminalis and the atrium. It measured 4 by 0.5 mm., the long axis being parallel to the pericardium. The shape was roughly triangular, except that the angles were much rounded off. The structure of the node, aside from the abnormalities noted, was normal, both in the total quantity of muscle present and in the relation of this amount to that of connective tissue. An unusual arm projected outward from its left border toward the pericardium, continued parallel with it a short distance and was finally lost in the muscular structure of the auricle. At a level still lower, the node measured 6 by 1 mm. and lay only 0.5 mm. from the pericardium. The largest proportions the node attained were 6.5 by 1.5 mm., 13.74 mm. from the upper extremity. From this point onward, the dimensions of the node became rapidly reduced and the structure terminated in a tail, the larger part of which was formed of connective tissue.

The relation of muscle to nerves and ganglia was unusually close. At all levels there were collections of ganglion cells in the space between the pericardium and the muscle layer. Nerve bundles, both small and relatively large, were found in the same situations and also within the structure of the node itself. About the nerve ganglia and nerve fibers the new-formed, thin-walled blood-vessels, which have been described, were found in rather large numbers. The artery, which is so often found in relation to the node, had at a low level a distinct reduction in the diameter of the lumen, due to an endarteritic process. This vessel showed no other point of interest except collections of smooth muscle fibers arranged in bundles and irregularly distributed about the vessel as an external longitudinal layer, similar to that which has been observed to lie about the central venous sinuses of the adrenal glands.

The Conduction System: The block containing this system was excised in the usual manner. It was cut in sections 12 microns thick in a plane at right angles to the long axis of the heart. Every fifth section was mounted. In the interauricular septum both muscle tissue and fat showed the presence of many leukocytes and lymphocytes in groups and also lying between the strands of muscle fibers. The auriculonodal junction was of sufficient size but was inflamed. The auriculoventricular node was of normal size, large rather than small, showing the characteristic interlacing of the fibers, but poorer in nuclei than is usual. There was a fairly well marked inflammatory process of the nature described and also moderately large collections of inflammatory cells within the substance

2. Heart, 1911, ii, 245.

3. The length of the node in another heart weighing 899 gm., already reported (Heart, 1912, iv, 24) measured 21.55 mm. Koch (*Med. Klin.*, 1911, No. 12) gives the length as about 3 cm., but cites no specific examples.

of the node. A similar inflammatory lesion was also found near the beginning of the main stem. It lay just outside the bundle and extended a short distance along the sheath. It did not compress the bundle. The main stem was large, well-developed, normal in appearance and intact from auricles to ventricles. Just before the division of the main stem into the ventricular branches, there was another area showing an infiltration with leukocytes and lymphocytes. From the point of division onward, the branches, more especially the right, showed only slight inflammatory lesions. Both branches were normal in size, the right a little larger than the left at the beginning.

Résumé: The sino-auricular node showed normal relations between the amounts of connective tissue and muscle; there was no sclerosis, but an inflammatory lesion in slight part within the substance, but for the most part without, though in the neighborhood of the node. The auriculoventricular node was inflamed to a far greater extent than the sinus node and contained abscess-like bodies. Similar smaller collections were found in the main stem. Congestion was a marked feature of the lesion throughout. There was no break in continuity of the conduction system.

DISCUSSION AND SUMMARY

A case is described in which, while the patient was under observation, a sequential rhythm changed to complete irregularity of the cardiac mechanism, due to auricular fibrillation. It is extremely doubtful whether the one-half drachm of digitalis which the patient received could have been responsible for the altered rhythm, even if she had been given the drug before admission to the hospital, five days before. Neither can the fall in ventricular rate from 120 to 80, occurring with the onset of fibrillation, be ascribed to an administration of digitalis extending over only half a day. The fall in rate occurring with the onset of auricular fibrillation is difficult to explain, but it occurs in other conditions of which we have only slight knowledge. The action of strophanthin administered intravenously was studied and showed a strikingly beneficial effect on the circulation and the subjective symptoms of the patient. The post mortem examination showed a lesion of the sino-auricular node, but it cannot be definitely asserted that a relation exists between the lesion described and the clinical irregularity that was studied.

THE RELATION OF HEART-BLOCK TO LESIONS OF THE AURICULOVENTRICULAR BUNDLE, WITH REPORT OF A CASE*

HAROLD E. B. PARDEE, M.D.
NEW YORK

In view of the present interest in the relation of demonstrable anatomical changes in the auriculoventricular conduction system to the changes in the function of this system, the present case may be found of interest. It will serve as an instance of how extensive the anatomical disturbance of the bundle may be without destruction of its function.

CASE REPORT

History.—The patient entered the New York Hospital March 18, 1912, on the service of Dr. L. A. Conner, to whose kindness I am indebted for permission to use the case. He was an Italian laborer, aged 23. Venereal infection was denied, nor was there a history of secondary or tertiary syphilitic manifestations. He had used considerable beer and whisky for the last four or five years. He had never had chorea or any rheumatic manifestations. He had had typhoid fever in late childhood, but otherwise had always been healthy until the present illness.

Three months before admission to the hospital, both knees became painful, swollen and tender, and shortly afterward his wrists, hands, shoulders and ankles were similarly affected. He felt feverish, had considerable headache, and perspired freely. He was very weak and so prostrated that he remained in bed. Soon after the onset of the joint symptoms he began to be troubled by palpitation and moderate shortness of breath, and there was also a slight dry cough. His condition had remained about the same until admission to the hospital.

Examination.—On admission at 12 m., his rectal temperature was 98.4 F. his pulse 82 per minute, and his respirations 20 per minute. He seemed normal in appearance, but slightly dyspneic. The skin and mucous membranes were both pale and slightly subicteric. The eyelids were slightly edematous, the sclerae faintly subicteric. His radial pulses were equal, regular, full and of good tension. The vessel wall was slightly thickened; the pulse wave seemed to have a slow, strong impact and a slow fall. There was no venous engorgement.

The cardiac impulse was felt diffusely in the fifth and sixth spaces, the maximum impact being in the sixth space, 13 cm. to the left of the mid-line. The action was strong and heaving, 84 beats per minute and regular. Cardiac dulness extended to the right of the mid-line, 3.5 cm. in the fourth space, and to the left of the mid-line 15 cm. in the sixth space, 12 cm. in the fifth space, 8.5 cm. in the fourth space, 7 cm. in the third space, and 2.5 cm. in the second space. A fine systolic thrill could be felt over the upper part of the sternum and in the vessels of the neck. The first sound at the apex was loud and booming and accompanied by a blowing systolic murmur of moderate intensity, well transmitted to the left. The second sound was followed immediately by a low-pitched, rumbling murmur which ran through all of diastole except for a very brief pause before the first sound. These signs were localized over an area about

* Submitted for publication, April 10, 1913.

5 cm. in diameter about the apex impulse. Outside of this area loud blowing systolic and diastolic murmurs were heard. At the base was a loud, rough systolic murmur, best heard to the right of the sternum in the second space, transmitted in all directions, and heard in the vessels of the neck. There was also a loud blowing diastolic murmur, heard best to the left of the sternum in the third space, but transmitted all over the precordium.

There was no deformity of the bony thorax. The lungs showed no abnormal signs. The abdomen was soft and not distended, but was slightly tender in the region of the epigastrium. Liver dulness extended from the sixth rib to the costal margin in the mid-clavicular line. The edge was indistinctly felt 5 cm. below the tenth rib and was not tender. The spleen was not made out to be enlarged. The inguinal lymph-nodes were slightly enlarged and soft, but elsewhere the nodes were not enlarged. The fingers showed faint capillary pulsation and a moderate degree of clubbing. No pistol shot sound was heard over the femoral artery. Both wrists and ankles, though not swollen or reddened, were slightly painful on movement and tender to pressure. Both knees were moderately swollen, tender and painful but not reddened. They contained some fluid and thickened synovial fringes. The legs below the knees were slightly edematous. The blood showed hemoglobin 64 per cent. (Sahli), white blood corpuscles 17,700, polymorphonuclears 84 per cent., mononuclears 13 per cent., eosinophils 2 per cent., basophils 1 per cent. The urine contained a very faint trace of albumen, but no casts.

Management and Course.—During the next forty-eight hours the temperature varied from 99 to 101 F. The pulse, 96 and 90 beats per minute on the day of admission, was 80 during the next day and 72 on the morning of the third day. It was always regular, and the rate remained quite uniform, showing no abrupt variation, only, as noted, a gradual slowing.

He was kept continuously in bed. Beginning on the morning of March 19 he was given 30 grains of sodium salicylate and the same amount of sodium bicarbonate every four hours. During the night of March 19 he perspired profusely. On the morning of March 20 his condition was noted to be improved. There was practically no dyspnea and the joints were less painful.

At about 4 p. m. on March 20, the patient complained of feeling very weak and became very pale. He said he had never had such an attack before. The radial pulse was imperceptible, the carotid pulsations and apex beat being 36 to the minute. The cardiac dulness and murmurs were unchanged. There was no venous engorgement. The patient was lying in bed and complained of no dyspnea or faintness, but felt a slight precordial discomfort, some pain in the epigastrium and great weakness. At 5:15 he was given 1/50 grain of atropin sulphate by hypodermic, but without appreciable effect on the symptoms or pulse.

From the onset of the attack the patient's condition remained unchanged, the symptoms being few and mild. At 7:15, however, he became very dyspneic and restless and had the appearance of moderately severe shock. The cardiac dulness now extended 4.5 cm. to the right and 16 cm. to the left in the sixth space, though the murmurs were unchanged. All over the lungs were heard very many fine and medium moist râles and he soon began to cough up small amounts of thin bloody fluid containing very little mucus. At 7:30 he was given 1/15 grain of strychnin sulphate by hypodermic and the foot of his bed was raised. He continued dyspneic, coughing up bloody material, though less restless, and at 9 p. m. was given ¼ grain of morphin sulphate and 7 grains of caffein sodio-salicylate by hypodermic. At no time was his radial pulse palpable, though the heart continued to beat at the rate of 30 to 32 per minute.

At about 10 p. m. his heart action became irregular, the irregularity consisting in the frequent occurrence of coupled beats. He seemed to be much better at this time, being no longer restless and having less cough and dyspnea. The râles in his lungs were also less numerous. From 10 p. m. until 1:30 a. m. he continued

to improve; the cough was less frequent and his discomfort less. The carotid pulse was still slow and continued to show coupled beats. From 2 to 5 a. m. the patient slept. On awakening at 5 a. m. his brachial pulse was recorded by the nurse as 29 per minute, and his respirations as 24 per minute. He seemed to be in good condition and did not complain of any discomfort. Shortly after this he was seen to sit up in bed and reach out for something beside him. He suddenly cried out, and fell back clutching at his precordium and was found to be dead.

Fig. 1.—Jugular and carotid pulse-tracings showing complete heart-block; auricles 69.5 per minute, ventricles 31.5 per minute.

A polygraphic record of the jugular and carotid pulses, taken at 4:30 p. m., shortly after the onset of the attack, showed that complete auriculo-ventricular dissociation was present (Fig. 1). The auricular rate was 69.5 per minute, the ventricular rate 31.5 per minute. In Figure 2, taken at 5:45 p. m., one-half hour after the administration of the atropin, the dissociation was still complete. The auricular rate had increased to 98.4 per minute and the ventricular rate to 34.4 per minute.

Fig. 2.—Tracing obtained one-half hour after atropin. Complete block still present. Auricles 98.4 per minute, ventricles 34.4 per minute.

In a tracing taken two hours after the atropin had been administered, and which it does not seem necessary to reproduce, some of the vagus tone had been regained, for the auricles had slowed to 85.9 per minute and the ventricles to 32.1 per minute.[1]

1. It is of interest to note that though the auricular rate showed the most marked result from the paralysis of the vagus endings, still the ventricles seemed also to be affected, though to a much less extent.

Figure 3 is a curve taken at 10:30 p. m., shortly after the onset of the arhythmia. No definite auricular waves have been demonstrated in this jugular curve, but it is not felt that this must prove their absence, in view of the distortion of the curve by respiratory waves, and of the fact that even the ventricular waves are not well marked. The carotid curve shows that what would otherwise be a slow regular rhythm of 33.6 per minute is five times irregularly interrupted by beats following the rhythmic beats at intervals of 0.75 second, 0.84 second, 0.60 second, 0.82 second and 0.82 second. In each case the interrupting beat is followed by a pause of the period of the rhythm; i. e., about 1.80 seconds, except in the one instance in which the interrupting beat follows after 0.60 second, and here the succeeding pause is slightly shorter than the rhythm interval. If this coupling were due to the second beat being the result of a stimulus transmitted from a coordinately contracting auricle, we should expect to find a wave due to the auricular contraction occurring at approximately the same interval before each of these beats. We should further expect that the time intervals between these interrupting beats would be multiples of some smaller figure representing the auricular rate.

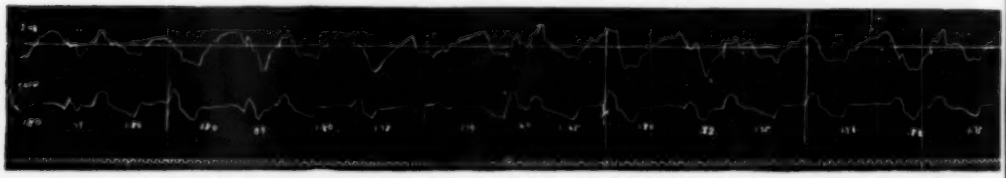

Fig. 3.—Tracing obtained after onset of arhythmia, considered to show interruption of the ventricular rhythm of heart-block by ventricular extrasystoles. Figures below carotid curve represent the pulse interval in .01 second. The timer marks 1/5 second.

As neither of these conditions is fulfilled, it is not believed that the auricle is responsible for their occurrence. The facts could be best explained if complete heart-block were still present and the arthymia were due to ventricular extrasystoles.

PATHOLOGICAL EXAMINATION

Permission was obtained for only a partial autopsy. The findings, reported by Dr. William J. Elser, were as follows:

"The pericardial sac contained 30 c.c. of clear serous fluid. The heart is moderately enlarged and all the chambers distended by partially clotted blood. The enlargement is due to dilatation and hypertrophy of the left ventricle. The other chambers are moderately dilated. The myocardium is pale red in color, opaque in appearance and of about normal consistence. There are no distinct focal lesions. The mitral valve is normal in appearance; the mitral orifice does not seem to be enlarged. The aortic valve shows the typical lesions of malignant endocarditis. All the cusps are covered with a large yellowish-white

vegetation composed chiefly of fibrin. The substance of the heart has been eroded. The corony arteries are normal. The arch of the aorta is normal. The pulmonary and tricuspid valves are normal. The lungs appear to be edematous. A blood culture made at autopsy from the left median basilic vein was negative.

"A portion of the aortic vegetation was removed and thoroughly washed in sterile water. It was then crushed and agar plates made from it showed the growth of an organism which proved to be streptococcus logus."

The heart was immediately fixed in formaldehyd-Müller's solution, washed and placed in alcohol. After fixation the breadth of the auriculoventricular groove posteriorly was 9.5 cm. The distance from the auriculoventricular groove to the apex was 14 cm. anteriorly and 10 cm. posteriorly. The thickness of the wall of the left ventricle varied from 1.6 cm. to 1.8 cm.; that of the right ventricle from .4 cm. to .6 cm. The papillary muscles of both sides were well developed, that of the left ventricle especially so.

The aortic valves were markedly involved in the process described, as can be seen from Figure 4, a photograph of the block excised for microscopical

Fig. 4.—The block removed for section of the auriculoventricular system viewed from the left side. M = cut edge aortic cusp of mitral valve. RP = right posterior cusp of aortic valve. A = anterior cusp of aortic valve. LP = left posterior cusp of aortic valve. X = small aneurysm of the wall of the aorta just above the level of the aortic valve. S — S = plane of section. The course of the node and bundle is indicated by the mark below the right posterior aortic cusp.

examination of the auriculoventricular bundle. The left posterior cusp was least involved; the anterior cusp was most involved. Both the anterior and the right posterior cusps were markedly thickened and the sinuses of Valsalva were almost obliterated. The heart tissue behind and below these cusps was also involved and was markedly calcified as was the tissue filling in the sinuses of Valsalva. The area of calcification below the anterior cusp extended downward in the muscle of the interventricular septum for 10 mm., bulging beneath the endocardium, 4 mm. at the upper part, and 2 mm. at the lower. The calcification did not appear to extend below the lower limit of the right posterior cusp.

Microscopical Examination.—Pieces of tissue were removed for microscopical examination as follows: (1) a portion of the wall of the right auricle so as to include the sino-auricular node; (2) other portions of the wall of the auricles; (3) the portions of the interauricular and interventricular septa which include the auriculoventricular system from the node to well beyond the branching (Fig. 4); (4) portions of the outer walls of the ventricles, and (5) portions

of the base of the papillary muscles. The blocks containing the sinoauricular node and the auriculoventricular system were imbedded in celloidin-paraffin and cut in serial sections. The other tissues were cut with the freezing microtome.

The walls of the smaller arteries and arterioles throughout the heart did not seem abnormal. The capillaries were everywhere distended with blood and in places small extravasations had occurred into the tissues. The cardiac muscle in the left auricle and especially in the left ventricle and in the interventricular septum showed a diffuse increase in the cells of the interstitial tissue, these being for the most part round cells though there were many endothelial and polymorphonuclear leukocytes. In the left ventricle, and especially in the septum, were patches of old myocarditis where the muscle fibers were entirely destroyed. These areas contained many fibroblasts and an increased amount of connective tissue fibrils, but no leukocytes. These areas were especially numerous and extensive at the basal part of the interventricular septum. The muscle of the right auricle and ventricle was more normal, showing but a small number of

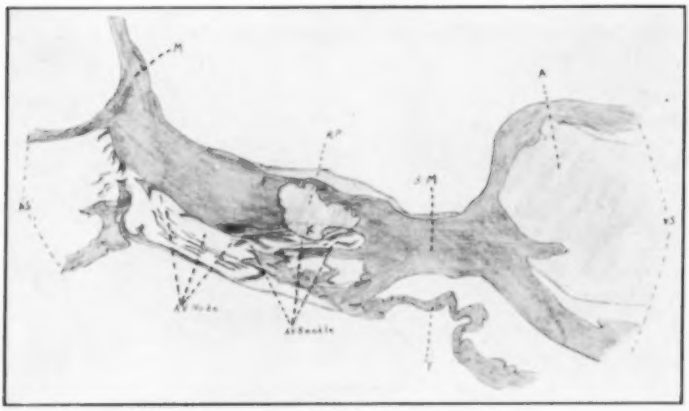

Fig. 5.—Projection drawing of a section showing at X the probable extent of destruction of bundle tissue. Fibrous tissue is black. Muscle tissue white. Necrotic material shaded. AS = auricular septum. M = mitral valve. RP = necrotic focus below right posterior aortic cusp. SM = septum membranaceum. T = tricuspid valve. A = necrotic focus below anterior aortic cusp. VS = ventricular septum.

round cells in the interstitial tissue and only an occasional leukocyte. The papillary muscles showed a few round cells in the interstitial tissue, and the muscle fibers beneath the endocardium were markedly vacuolated so that the sarcoplasm was at times almost entirely gone from the central part of the fiber, leaving the nucleus supported by strands extending in from the periphery. The nuclei seemed unchanged. The sino-auricular node seemed to be normal, though possibly the fibrous tissue was very slightly increased in amount. The fibers were well striated and there were no leukocytes found here.

Very marked and extensive changes were found in the auriculoventricular system. At 3 mm. beyond its origin from the node, the auriculoventricular bundle became involved in the extensive focus which has been described involving the right posterior aortic cusp. This focus extended into the central fibrous body of the heart between the attachment of the anterior cusp of the mitral valve below and posteriorly and the septum membranaceum above and anteriorly, but lying nearer to the former than to the latter. It extended in the fibrous

body from the upper level of the right posterior aortic cusp, downward to the upper level of the interventricular septum, lying just beneath (to the right of) the endocardium of the aortic vestibule. The tissue involved was necrotic and in part calcified. For 3.3 mm. of its course the bundle passed along the right aspect of this focus — the side away from the endocardium — and became involved in it so that about one-half of its thickness was destroyed. The conditions may be better understood by a reference to Figure 5, in which the probable extent of the destroyed tissue is indicated, and to Figure 4, in which the course of the bundle is marked as if seen through the heart tissue. The non-calcified areas of this focus were thickly infiltrated with round cells and polymorphonuclear leukocytes and this cellular infiltration extended into the adjacent tissues; into the fibrous tissue of the central fibrous body, into the muscle of the auricular septum above, into the muscle of the ventricular septum below and into the auriculoventricular bundle where this crosses through the fibrous body from right to left.

Thus, besides the actual destruction of the tissue of the bundle, which must from the nature of the changes have been of considerable duration, there were indications of a more acute process throughout the bundle and the node. This was probably caused by the streptococcus which was affecting the neighboring valve. There was a diffuse and marked infiltration by polymorphonuclear and endothelial leukocytes with a large number of fibroblasts. This infiltration was most marked opposite to the eroded portion of the bundle and here the polymorphonuclear cells were in excess. Elsewhere mononuclear cells predominated. In the neighborhood of areas of dense connective tissue the fibroblasts seemed to be especially numerous so that the infiltration was very marked along the left aspect of the auriculoventricular node where it lay against the central fibrous body and in the latter course of the bundle and in the right branch, where the fibrous tissue septa were more numerous. The infiltration by leukocytes and round cells extended into the main branches of the bundle, and was well marked as far as these were followed. The node and the portion of the bundle beyond the erosion seemed to be edematous. The communication between the auricle and the node was uninterrupted though involved in the inflammatory process.

DISCUSSION

We may consider, then, that when the patient first came under observation, his auriculoventricular conducting system was functionating normally, or at least that impulses were being transmitted regularly from auricle to ventricle.[2]

In accordance with this, his pulse was regular and became slower under the influence of rest in bed quite as was to be expected. He then developed complete auriculoventricular dissociation, which persisted after the vagus was paralyzed by atropin, and continued for thirteen hours until his death. Post mortem examination showed that the auriculoventricular bundle was involved in a chronic destructive process, and besides this, both node and bundle showed an extensive diffuse acute inflammation.

2. Though it cannot be denied that the patient may have shown lesser degrees of heart-block, i. e., dropped beats, or increased conduction time, before the period of observation began, this is not considered to be probable. In support of this assumption is the fact that he was free from arhythmia for fifty-two hours before complete dissociation set in — the time when a latent tendency to block would have been most likely to become evident.

The point to be emphasized here is that though the diffuse acute inflammation resulted in complete auriculoventricular dissociation, yet the bundle had been extensively involved in a chronic process — only one-half of its transverse section remaining throughout about 2 mm. of its course. Though it had been in this condition for weeks, or more probably for months, yet the patient had never had symptoms which would lead us to believe that it had ceased to function, and moreover he showed no signs of heart-block for fifty-two hours before complete dissociation supervened.

Following the very interesting results which Erlanger obtained by compression of the auriculoventricular bundle, in which the degree of functional disability seemed to be parallel with the degree of trauma, attempts were made to correlate with these results the post mortem findings from clinical material. These attempts have been successful in one particular. No cases of complete destruction of a transverse section of the bundle have been reported in which there was not complete auriculoventricular dissociation. Ten such cases have been found in the literature: Bönniger and Mönckeburg[3] report two cases, Heinecke, Müller and Hösslein,[4] Monrad Krohn,[5] Nagayo,[6] Vaquez and Esmein,[7] Fahr[8] and Cohn and Lewis[9] each report one in which the condition of the bundle was shown by serial sections. Jellineck, Cooper and Ophüls,[10] and Oddo and Sauvan[11] have reported cases in which an extensive infarct and a hemorrhage, respectively, involved the septum in the bundle region and must surely have included it. The cases of Armstrong and Mönckeberg[12] and of Cohn and Lewis[13] should be included in this group for a lymphangio-endothelioma in the one case, and an aneurysm in the other, was found in the auricular septum, completely separating the node from the auricular musculature and inducing complete auriculoventricular dissociation.[14]

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3. Bönninger and Mönckeburg: Deutsch. med. Wchnschr., 1908, No. ii, 298.
4. Heincke, Müller and Hösslein: Deutsch. Arch. f. klin. Med., 1908, xciii, 459.
5. Krohn, Monrad: Arch. de mal du coeur, 1911, iv, 350.
6. Nagayo: Ztschr. f. klin. Med., 1909, lxvii, 495.
7. Vaquez and Esmein: Bull. et mém. Soc. méd. d. hôp. de Paris, 1907, Series 3, xxiv, 78.
8. Fahr: Virchow's Arch. f. path. Anat., 1907, clxxxviii, 562.
9. Cohn and Lewis: Heart, 1912, iv, 15.
10. Jellineck, Cooper and Ophüls: Brit. Med. Jour., 1908, i, 796.
11. Oddo and Sauvan: Marseilles méd., 1907, xliv, 443.
12. Armstrong and Mönckeberg: Deutsch. Arch. f. klin. Med., 1911, cii, 144.
13. Cohn and Lewis: Heart, 1912, iv, 15.
14. The case of Cohn and Lewis is mentioned twice here since it showed both complete interruption of continuity of the bundle and complete separation of the node from the auricular muscle.

Opposed to these findings, six cases have been reported in which serial sections have shown that there was no lesion of the conducting system though various degrees of block were present before death. In the cases of Fahr,[8] Krumbhaar,[15] of Price and Mackenzie[16] and of Holst and Krohn,[17] the block was complete. In that of Mollard, Dumas and Rebattu[18] it was partial, while in that of Monrad Krohn[5] the degree was not definitely stated, but was probably complete.

Intermediate degrees of bundle involvement have been found in cases showing both partial and complete heart-block. Some of them have shown very considerable lesions of the bundle with marked destruction of its tissue due to chronic inflammatory processes, and these cases have shown the higher grades of block, usually complete. Where still less marked pathological changes were found, almost minimal at times, complete heart-block has been present in six cases and partial block in four. These are tabulated with their histological changes in detail for more ready comparison.

CASES SHOWING COMPLETE HEART-BLOCK

Cohn, Holmes and Lewis: Node is normal except for a few strands of dense hyaline connective tissue and a moderate amount of fatty infiltration. The bundle is invaded by dense strands of connective tissue from the septum membranaceum. There is moderate fatty infiltration of the bundle. Large blood sinuses seriously reduce the diameter of the bundle but there are no signs of an inflammatory origin of these. The connective tissue within the bundle is increased. Heart, 1911, ii, 241.

Herxheimer and Kohl: The node shows a slight increase in connective tissue and a few round cells between the fibers. The bundle shows no change, but the fibrous tissue of the septum membranaceum is in part calcified. Deutsch. Arch. f. klin. Med., 1910, xcviii, 330.

Pibram, Koch and Kahn: The artery to the septum shows hyaline degeneration of its wall and in the neighborhood of this the node is somewhat sclerotic. There is an evident increase in fatty tissue in the node and bundle and there is an area of lymphocytic infiltration in the bundle. The muscle fibers of the node and bundle appear normal. Berl. klin. Wehnschr., 1910, xlvii, 1108.

Flemming and Kennedy: Node and first part of bundle involved in a well-marked inflammation. Show markedly congested capillaries and a few foci of round cells mostly lymphocytes, but a few large mononuclear cells of fixed tissue origin. One large focus in beginning of bundle, mostly lymphocytes, but a few large mononuclear cells and some polymorphonuclear leukocytes, appears to damage the fibers passing through it. There are a number of similar foci in auricle bordering on node. These lesions do not involve a great extent of bundle tissue. Heart, 1910, ii, 77.

Beck and Stokes: Bundle beset by numerous hemorrhages and its branches show moderate purulent infiltration. The bundle fibers are separated and surrounded by connective tissue containing many fibroblasts, lymphocytes and a few polymorphonuclear leukocytes. Jour. Am. Med. Assn., 1910, lv, 1065.

Hay and Moore: Artery to node and bundle is atheromatous. There are patches of a recent inflammatory process where the bundle perforates the central

15. Krumbhaar: THE ARCHIVES INT. MED., 1910, v, 583.
16. Price and Mackenzie: Heart, 1912, iii, 233.
17. Holst and Krohn: Quart. Jour. Med., 1911, iv, 498.
18. Mollard, Dumas and Rebattu: Arch. d. mal, du coer., 1911, iv, 298.

fibrous body — cells resolving into fibroblasts. This process is patchy in distribution and does not extend throughout the whole bundle. Lancet, London, 1906, ii, 1271.

CASES SHOWING PARTIAL HEART-BLOCK

Gerhardt: The part of the bundle which crosses through fibrous body shows normal muscle fibers, but an extensive cellular infiltration most marked in the immediate neighborhood of the blood vessels. The larger vessels which enter the bundle show a marked thickening of the interior so that the lumen of the larger vessels is markedly narrowed. Deutsch. Arch. f. klin. Med., 1908, xciii, 485.

Griffith and Cohn: Endarteritis of vessels of node and septum diminishing their caliber so that some are entirely occluded. Scattered groups of lymphocytes in interventricular septum about node and to less extent within it. Connective tissue strands separating muscle bundles of main stem. In portions of bundle "granulation tissue with numerous lymphocytes." Diameter of bundle reduced and fibers compressed. Quart. Jour. Med., 1910, iii, 126.

Cowan, Kennedy, Paterson and Teacher: Well-marked congestion of node and bundle. Three foci of round cells within bundle, all fairly small, cells mostly lymphocytes, but a few larger new connective tissue cells. Fibers of bundle show degeneration in neighborhood of two larger foci, but are otherwise normal. Quart. Jour. Med., 1911, iv, 35.

Butterfield: The node is deeply involved in the morbid process (general acute inflammation of heart substance), particularly in neighborhood of fibrous body where the normal appearances were completely obscured by a dense cellular infiltration of lymphocytes, leukocytes and large mononuclear cells. Throughout the remainder of the node and bundle every vessel was surrounded by an infiltration composed almost entirely of lymphocytes. Heart, 1912, iii, 233.

It is always necessary, in comparing the histological reports of different observers, to bear in mind the varying importance which may be ascribed to certain findings; in this instance as to whether the amount of fibrous tissue or of fatty tissue exceeds the normal and whether distended capillaries signify anything more than ante mortem or post mortem stasis. The node and bundle lie in proximity to the fibrous ring, which besides forming a sheath about the bundle and its branches, sends dense septa into them; while the node has a loose reticular structure the spaces of which are occupied by connective tissue fibrils. Both node and bundle normally contain a certain number of fat cells, and these are known to vary in amount with age,[19] and presumably vary also with individuals. Referring then to Note 19, it is seen that the pathological changes of those cases showing complete dissociation are not more marked than of those showing but partial dissociation. In fact, all of the cases in the second group of partial block show more marked changes than the first three in the first group of complete block.

The present case, considered before the onset of the acute inflammation, is the only one so far reported in which there was extensive destruction of bundle tissue without evidences of heart-block. The

19. Mönckeberg: Untersuchungen über das atrio ventricular Bündel, Jena, 1908.

explanation of this is thought to lie only in the fact that the auriculoventricular system is not usually examined unless there are evident signs of heart-block.

CONCLUSIONS

From a consideration of the above facts it is believed that complete or very extensive destruction of the tissues of the conducting system will result in complete heart-block. Lesser degrees of destruction or varying degrees of involvement of the tissues in other pathological processes, such as fibrosis, lymphocytic, leukocytic or fatty infiltration, may produce (1) complete heart-block, (2) partial block with 2 to 1 or 3 to 1 rhythm or dropped beats, or (3) as in the present case, no block at all. It appears that the cases with the higher degrees of block do not necessarily show marked lesions, and *vice versa*, and that, moreover, complete dissociation may occur with no demonstrable changes in the conducting system.

Clinically, then, the functional capacity does not vary solely with the extent or severity of the anatomical changes in the auriculoventricular node and bundle; a result, indeed, which might be expected from a consideration of the pathological physiology of other organs. This statement is not considered as at all contrary to Erlanger's results, for, since these were obtained in healthy animals, the trauma was the only factor affecting the junctional tissues.

As to what the clinical factors are which influence this functional capacity, we know very little. We know, however, from animal experimentation, that certain drugs, as well as asphyxia and increased activity of the vagus nerve, possess the power of depressing it. By analogy it might be supposed that the toxins of pathogenic bacteria or of faulty metabolism, or a deficient blood-supply (local asphyxia?), due to endarteritis or to a failing circulation would also affect it. The case of Price and Mackenzie,[16] in which complete heart-block developed in the course of diphtheria, as well as Krumbhaar's[15] case, which followed typhoid fever, are believed to be instances of the toxic type. Though numerous cases have been reported as occurring in the acute infectious diseases as well as in malaria and diabetes mellitus, still, as they have not been accompanied by autopsy reports to prove the bundle to be intact, we can obtain from them only presumptive evidence of the action of the respective toxic substances. No instance has been found in which endarteritis could be ascribed as the sole cause of heart-block on account of the fibrosis which keeps pace with this process. The observation of Robinson,[20] that some degree of heart-block was present in five of seven cases in which records were taken of the dying heart, is considered an instance of the circulatory type as well as the fact, often noted in the

20. Robinson: Jour. Exper. Med., 1912, xvi, 291.

wards, that patients showing partial block when in a poor state of compensation often fail to show this when their condition has improved. It is questionable if vagus activity can be sufficiently increased clinically to be the sole cause of heart-block, though its action in the case of digitalis on a predisposed heart is well known. No conclusive case of this type has so far been reported.

SUMMARY

1. A patient with aortic and mitral insufficiency and normal heart action developed complete heart-block and died.

2. Autopsy showed a streptococcus endocarditis superposed on a chronic process of the aortic valve which had involved the substance of the heart.

3. The auriculoventricular bundle had been destroyed for one-half of its transverse section by the chronic process, but this, so far as known, had never produced heart-block.

4. Complete heart-block was produced by an involvement of the auriculoventricular system throughout its whole extent in an acute inflammation.

5. The extent of the lesion of the bundle in the cases which have been previously reported is contrasted with the degree of heart-block which was present at death.

6. It is concluded that the extent of the anatomical changes is not the only factor which induces heart-block.

7. Bacterial and metabolic toxins and deficient local blood-supply are suggested as accessory factors which, in certain circumstances, might act alone.

156 East Sixty-first Street.

THE CLASSIFICATION OF NEPHRITIS*

HORST OERTEL, M.D.
NEW YORK

Classifications of the so-called hematogenous inflammations of the kidney, commonly grouped as Bright's disease, have been made from five standpoints: 1. Etiological; 2, pathogenetic or histogenetic; 3, functional or physiological; 4, clinical (according to the symptom complex); 5, descriptive (a) according to the topography or (b) according to the predominating anatomical changes.

Attempts at correlation of several of these principles have also been made, particularly the clinical and anatomical and the etiological and pathogenetic classifications have been closely identified. But the difficulties and complications which are associated with these imperfect combinations have recently led to a desire for simple and uniform methods of classification.

An effort will be made in the following lines to present a critical review of these classifications, the evidence which has been advanced in their support and to draw attention to some erroneous anatomical and histological conceptions which have acquired importance in the discussion of renal diseases. Finally, I propose to discuss just how far a classification of these kidney lesions seems practically possible.

I.

I. THE ETIOLOGICAL CLASSIFICATION

The etiological classification of nephritis has not enjoyed much confidence and support on the part of the pathologists. It has never been adopted by the best known works on pathology or medicine. In 1905, however, F. Müller,[1] in his admirable review of Bright's disease before the German Pathological Society, revived interest it. Müller proposed substitution of an etiological classification for the present anatomical one for the reason that anatomical lesions are not within the possibility of actual observation by the physician. The etiological classification, however, may be based almost directly on the experience and observation at the bedside, and appears therefore better adapted for the needs of the clinician.

* From the Russell Sage Institute of Pathology, New York.
* Submitted for publication April 4, 1913.

1. Müller, Fr.: Morbus Brightii. Verhandl. d. deutsch, path. Gesellsch., 1905, ix, 64.

But Müller was conscious of the difficulty of this undertaking, for he added guardedly that such a classification could plainly be of use only, if the different intoxications and infections always produced characteristic changes in the kidney. In outlining this classification, Müller stated that it was based to a great extent on personal observations, and he was conscious that the chronic types of nephritis could not, on account of their complexity, be included in this scheme.

As was natural, therefore, Müller's recommendations were received with much reserve by both pathologists and clinicians. Indeed, collective experience points to the untenability of this principle, even for the so-called acute inflammations of the kidney.

It is true that in cholera and mercuric bichlorid poisoning the kidney changes are regarded by some as absolutely characteristic; but even if this should be true (and it has not been established beyond all doubt), these are the only two for which such a claim may reasonably be made. We know that the majority of all infections and intoxications does not show specific characteristics.

In a previous communication[2] I enumerated several years ago those infections, which, in my experience, may lead to anatomically similar lesions; these are the general and local streptococcus diseases: angina pharyngis, tonsillitis, otitis media and others; further, recent syphilis; the exanthemata and, contrary to general belief, pneumonia. Quite recently, Fahr[3] stimulated by Müller's remarks, after a more detailed investigation, arrived at very similar conclusions. It is interesting that he, as well as Kretzschmar,[4] apparently ignorant of my statements, also report the frequent occurrence of severe nephritis in pneumonia. Indeed, the high frequency observed by Kretzschmar has been doubted by others. But this difference of opinion may be explained by the fact that one and the same infectious disease, particularly if epidemic in its appearance, may at different times produce very variable results. In the New York epidemic of pneumonia, which occurred about five years ago with a high death rate, the disease manifested throughout a general septic character. It was associated with purulent pericarditis in an extraordinary degree (almost the rule at autopsy), and generally complicated by severe nephritis. In sporadic cases these are observed much more infrequently. The difference of opinion regarding the character of nephritis in pneumonia is undoubtedly due to the variety of lesions the disease produces under different conditions. Aschoff states that the pneumococcus causes

2. Oertel, H.: The Anatomic Histological Processes of Bright's Disease. Saunders Co., Phila. and London, 1910, p. 67.

3. Fahr: Können wir die Nierenkrankheiten nach aetiologischen Gesichtspunkten eintheilen. Virchow's Arch. f. path. Anat., 1912, ccx, No. 2 (Literature).

4. Kretzschmar: Cited by Fahr, Note 3.

a tubular nephritis. Müller also states that the epithelium only is involved and the glomeruli left free, while others report with equal positiveness the occurrence of interstitial and even hemorrhagic nephritis. I have been able to observe, by fortune of a large pneumonia material, the possibility of all these lesions. This example illustrates in regard to the pneumococcus and the kidney what has been known in regard to other organisms and organs, namely, that different etiological factors may produce anatomically similar lesions, but that the same etiological factor causes at different times very different lesions.

These experiences fully agree with the well-known observations of Asch[5] and others, that the structural and consequently functional changes in the kidney during an infection vary with the presence and location of bacteria and soluble or non-soluble toxins, which in one case may produce necrosis of the epithelium, in another exudation or interstitial leukocytic infiltration, or finally, a hyaline and amyloid degeneration of the vessel walls. To these must be added further the virulence of bacterial strains, the reactive ability and peculiarity of the individual and the mechanical conditions imposed by the structural arrangement of the kidney, which are very apt to influence the distribution of bacteria and toxins.

Finally, we must consider the importance of mixed infections. It is hardly necessary to discuss this well-known point in this connection. Everyone is acquainted with the influence which mixed infections exert on the manifestations of even etiologically well established diseases.

The true pathogenetic significance of the tubercle bacillus is as much under discussion in regard to the kidney as elsewhere. Senator held that the nephritis in tuberculosis was a chronic parenchymatous nephritis. Fr. Müller finds it sufficiently characteristic to separate it from other forms, and treats it as specific nephritis, while recently Fischer and Fahr[5] doubt entirely the existence of a tuberculous nephritis without mixed infection. Even if this latter view is deemed too radical it remains certain that in at least many instances it is impossible to separate the effects of the tubercle bacillus from those of the almost always accompanying streptococcus infection. Thus it would appear that the etiological classification is open to objection, even in diseases whose etiology has been established. Wherever the etiological classification has succeeded in entirely displacing anatomical conceptions it has led to much confusion. As example, our ideas of what is meant by diphtheritic or tuberculous inflammations are extremely indefinite, and really more confused than formerly, when simple descriptive terms were in more general

5. Asch: Ueber den Einfluss der bakteriallen Stoffwechselprodukte auf die Niere. Strassburg, 1904. L. Beust.

use. Etiological terms are insufficient unless qualified by others;[6] clearly then, the etiology alone can in no instance serve as a basis for classification.

II. THE PATHOGENETIC AND HISTOGENETIC CLASSIFICATION

The question whether inflammations of the kidney may be classified according to their genesis is both old and new. Two subdivisions of this question arise: first, is it possible to determine with sufficient accuracy the genesis of every nephritis, and secondly, does an established nephritis retain the features of its development sufficiently to give it a distinct anatomical and functional character. This last point is of great consequence to the physician, because he deals almost always with established inflammations. For instance, one would be justified to speak of parenchymatous nephritis if a nephritis which commenced with involvement of the parenchyma would retain the parenchymatous alterations to the exclusion or at least indisputable subordination of all other accompanying processes.

Virchow,[7] as is well known, combined a definite pathogenetic meaning with his ideas of parenchymatous nephritis. A parenchymatous inflammation represented to him a degenerative nutritive disturbance of cells excited by an excess of nutrient material. In his opinion, this controlled the whole inflammatory process; parenchymatous degeneration was the expression of inflammation. Virchow, therefore, had a perfect right to speak of parenchymatous inflammation, because he believed that the origin and course of the disease rested solely in the parenchymatous changes. On the other hand, his contemporary opponents in this matter championed, much like the older pathologists (Vogel's definition: inflammation = capillary hyperemia + hydrops fibrinosus), the interstitial vascular genesis and character of the inflammatory process. But they, like Traube for instance, employed their idea of inflammation in a manner similar to Virchow. For, while Traube differentiated between a circumcapsular and intertubular nephritis, he neglected and even denied any parenchymatous involvement. As early as 1860, Traube[8] declared with considerable pride that he had been the first to deny the existence of parenchymatous nephritis. In other words, the adherents of the genetic classification were divided, one might say, from the very start, and it may be added, from their standpoints justly so, because their ideas of the fundamental character of inflammation differed. These

6. See my discussion on cynanche contagiosa in the New York City Hospital Medical and Surgical Report I, 1909, p. 213 and ff.

7. Virchow: Ueber parenchymatöse Entzündung. Virchow's Arch. f. path. Anat., 1852, iv, 261.

8. Traube: Ueber den Zusammerhang von Herz und Nierenkrankheiten, etc., in Gesammelte Beiträge, ii, 970.

differences have become only more accentuated since. Indeed, Virchow was consequent enough and never regarded any interstitial process in nephritis as an inflammatory phenomenon, but as a process of repair. It will, therefore, be seen that the ideas of Aschoff in this regard are very similar to what Virchow held in 1852.

These views have never been reconciled by later investigators, although many attempts have been made from Rosenstein's[9] time to the present. Both ideas, Virchow's and Traube's, contained much truth, but not all the truth, and, as is not infrequent under such conditions, both were accepted and continued on authority of tradition unfortunately as *types* of inflammation instead of *evidences* of the inflammatory process. Thus originated and continued the contrast of parenchymatous and interstitial inflammations. Indeed, the most recent ideas of inflammation are as diametrically opposed as they ever were; while some still continue to speak of parenchymatous inflammation, although in a somewhat different sense from Virchow's, others have adopted a teleological conception; they regard, again, much like the older writers, only the reactive exudative changes as inflammatory and exclude all degenerative and proliferative changes entirely. This is opposed by a third group of pathologists, who hold that only the combination of, and intimate correlation of alterative, exudative and proliferative changes constitute inflammation. This group eliminates the conception of parenchymatous inflammation entirely and separates all nutritive and alterative changes from the inflammatory conception unless combined with exudative and proliferative changes. A last group of pathologists regards the inflammatory conception in a still broader and less restricted sense, purely objectively as the sum total of genetically closely related and allied processes which are the results of certain irritants and which present passive and reactive features in varying combinations. This is not the place to enter into the details or the merits of these opinions. They are mentioned here to demonstrate that not only in regard to the genesis of nephritis, but to the very nature of inflammation there exist wide differences of opinion which defeat any attempt at a genetic classification. On one point, however, pathologists agree to-day—that any established nephritis (possibly with the exception of the so-called interstitial nephritis) is a diffuse affection of all kidney structures, but in an uneven degree. Thus whatever views were held of the genesis of nephritis, the terms parenchymatous and interstitial acquired gradually a purely descriptive or topographical significance. This is best illustrated by Orth's[10] position. He states:

> . . . I hold it justifiable to speak of various forms of kidney inflammation, because the different constituents of the kidney are concerned in a most unequal

9. Rosenstein: Die Pathologie und Therapie der Nierenkrankheiten. 1863 and 1894.

10. Orth: Lehrbuch der speciellen pathologischen Anatomie. 1893, ii, 47.

manner. Following, therefore, the principle *"a potiori fit denominatio,"* I go so far as to acknowledge a parenchymatous, interstitial and glomerulonephritis. But it must be remembered that no sharp line of demarcation between them is possible, and that their combinations are frequent findings.

Fr. Müller, finally, makes the remarkable but true statement, that these terms are used at present not so much to designate an anatomical condition, but rather a clinical picture.

This confusion of uncertain teleological conceptions, anatomical terms and clinical pictures, has necessarily led to hopeless disagreement, and Heubner declares that the majority of cases of chronic nephritis in practice do not fit in the ordinary scheme and are atypical.

It has already been mentioned that Müller endeavored to introduce the etiological principle with the purpose of preventing further confusion, which is very apt to continue by the use of old or altered terms. But it has been seen that this latter offers no more hope for a useful classification than does the genetic one.

III. THE FUNCTIONAL OR PHYSIOLOGICAL AND CLINICAL CLASSIFICATIONS AND THE RELATION OF ANATOMICAL TO FUNCTIONAL CHANGES

Functional and clinical classifications of nephritis are strictly speaking not identical, although we shall consider them together for convenience sake. The functional takes into account only the altered kidney actions, while the clinical bases its views on the symptom complex; that is the sum total of all functional disturbances in the whole body which accompany or are resultants of the kidney disease.

It would appear from the start that both these methods of classification are beset with difficulties by reason of our limited knowledge of the normal kidney function and the even greater complexity and uncertainty of pathological functions and relations. Furthermore, the variability and lack of constancy on the part of the clinical symptoms would be an additional handicap to a clinical classification.

Nevertheless, both have acquired considerable importance lately, and an effort has been made to establish a functional differentiation of kidney disease. It must therefore be considered in some detail. In this connection we must first touch on certain erroneous conceptions which have resulted from a rather indiscriminate use of anatomical terms. It has become the custom to speak of vascular and tubular nephritis very much as formerly of parenchymatous and interestitial, in a contrasting sense, and to draw a sharp distinction between glomerulo and tubular nephritis. The most elaborate and ingenious distinction between the two forms the basis of Schlayer's views and those of his co-workers. Now it cannot be sufficiently emphasized that every nephritis, be it the product of poisons, or toxins, or whatever else, involves, if one considers time

and topographical action of irritants, all structures of the kidney. It is correct, however, that these structures are affected in an unequal quantitative and qualitative manner.[11]

In corrosive sublimate poisoning, for instance, the parenchyma cells suffer very severely and conspicuously from the beginning, but there exists also capillary hyperemia and edema. They are followed rapidly by cellular exudation and proliferation. Now it is held by some that these changes are primarily not inflammatory, but purely degenerative, and that this kidney lesion is a nephrosis and later an inflammatory nephrosis. In order to make this plausible it becomes necessary to disregard the capillary hyperemia in the beginning entirely and to look on the initial edema as non-inflammatory, but of a peculiar specific type. (Heineke and Marchand.[12]) Does this explanation not seem forced? Do we not come nearer an understanding of the actual occurrence if we regard each of these evidences as an integral part of a unit, namely, what is generally spoken of as inflammatory process? We may, if we please, treat the components of this process separately for the sake of study, but is it a gain to regard them as entities? They do not present themselves as independent processes, but occur in definite genetic progression and relation. Modifications in their appearance are due to time and topographical conditions rather than to deep-seated changes in character. It is, therefore, a mistake to assume that in what is described as glomerulo or tubular nephritis, or in a nephrosis only parts of the kidney suffer and others may escape. Nor can it be claimed that it adds to clearness to know that a patient suffers primarily from a pure nephrosis and shortly afterwards from an inflammatory nephrosis.[13]

But it may further be urged that there exist many kidney injuries due to toxins, etc., in which one of the important parts of the kidney — vascular or tubular—is relatively uninvolved. That is true, but it would be another error to conclude that relatively slight morphological changes are equal to negligible functional disturbances or that apparently well-defined morphological alterations are always equal to great functional disturbances. Pearce, who of the experimentalists is perhaps the most careful one not to lose touch with the morphological side of the question, showed with Eisenbrey[14] that nephrotoxic and hemolytic immune sera cause changes, which, by physiological methods, present no evidences of vascular injury, but which are anatomically characterized by exudative

11. A fuller discussion of this much disputed question may be found in my monograph: The Anatomic Histological Processes of Bright's Disease. Saunders Co., 1910, pp. 45 to 47 and pp. 63 to 67.

12. Heineke: Die Veränderungen der menschlichen Nieren nach Sublimatvergiftung. Ziegler's Beitr., xlv, 193; Marchand's remarks, *ibidem*, p. 241.

13. The definition of "nephrosis" is necessarily as uncertain as that of "nephritis," for the views on the nature of the latter determine those of the former.

14. Pearce and Eisenbrey: Jour. Exper. Med., 1911, xiv, p. 306.

glomerular lesions of moderate severity. Vascular, they say, must, therefore, be used in the broadest sense, and that lesions of the membrane controlling the passage of fluid may occur without alteration of the power of the vessel to contract and dilate. They differentiate three groups of functional and anatomical changes: 1. In which little or no anatomical evidence of vascular injury is found, but in which physiological methods show profound vascular changes (arsenic). 2. In which anatomical evidence of vascular (exudative) injury is prominent, but in which physiological tests are negative (hemolytic serum). 3. In which both are prominent (diphtheritic toxin).

These experimental investigations agree with similar clinical and anatomical evidences in human nephritis and demonstrate that the *quality* of morphological changes is of great importance in the relation of anatomical to functional changes. Aschoff has laid much emphasis on this point as we shall see later. It has been a general practice to employ solely a not too exact quantitative measure in the determination of structural changes and certainly an insufficient amount of attention has been devoted to their qualitative character. It may be argued that after a structure has been destroyed, it matters little how it happened. But in the first place important functional changes appear during early and slight changes in a structure, and secondly, destruction is very uneven, very rarely leading to complete annihilation of all cells composing a part. Qualitative structural alterations enter, therefore, into the functional changes throughout an observation.

A last important point, and one to which again an insufficient amount of attention has been paid in the experimental investigations of the kidneys, is the compensatory action of one part for another. We are well acquainted with it in the nervous system, we know a little of it in other organs like the hemapoietic and lymphatic systems and the liver, but in the kidney we are further from understanding it, although observations indicate that it exists in this as in other organs.

These general difficulties of a functional classification are further complicated in particular by the different results and views on the toxic effects of poisons.

The importance of this phase of the subject and the general interest and enthusiasm which has been aroused in it after the brilliant observations of Schlayer, Takayasu, Hedinger and Volhard, demand a somewhat detailed review of their work.

Schlayer and his co-workers[15] base their ideas on a strict division of vascular and parenchymatous injury as revealed by the excretion of

15. Schlayer and Hedinger: Experimentelle Studien über toxische Nephritis. Deutsche. Arch. f. klin. Med., 1907, i, 90; Schlayer: Untersuchungen über die Funktion kranker menschlicher Nieren. Kongress für innere Medizin, 27 Kongress, 1910, p. 744; Hedinger: Experimentelle Studien über die Wirkungsweise von Nieren und Herzmitteln auf Kranke Nieren. Ibid, p. 735.

water, sodium chlorid, potassium iodid and milk-sugar. Their experimental investigations have lately been supplemented by observation on human renal disease. Schlayer's experimental work showed that when the tubular cells were destroyed the excretion of NaCl and KI was correspondingly interfered with, while vascular injury led to interference with the excretion of milk-sugar. Urine concentration or water excretion may be influenced in two ways: By tubular injury, which diminishes the amount of solids; or by a hypersensitiveness of the blood-vessels, which increases water secretion: tubular or vascular hyposthenuria.

Sodium chlorid is not eliminated in the tubular nephritis, hence the urine concentration is low; on the other hand, sodium chlorid is fully eliminated in the vascular type; therefore concentration is constant and high, for the blood-vessels are hypersensitive.

In human oliguria the milk-sugar excretion is slow, while that of NaCl and KI is normal; it is, therefore, vascular in character. He considers polyuria due to sensitiveness of the blood-vessels. In scarlet fever nephritis the water is increased on account of vascular irritation, while the milk-sugar excretion is decreased; in other words, the vascular activity of the kidney has become disassociated.

The same underlying conditions are found in contracted kidney. It resembles, functionally, the acute vascular nephritis in a disassociation of its vascular activity, i. e., the injury to the blood-vessels manifests itself by an increase of water elimination and diminution of milk-sugar excretion. While, however, the acute nephritis shows both a diffuse anatomical and functional involvement of blood-vessels, the early stages of contracted kidney present, according to Schlayer, a diffuse functional injury when the anatomical picture still reveals only patchy disease. These observations and ingenious deductions are very interesting, but it may be justly doubted whether such findings, even if substantiated by further observations, furnish a sufficient basis for classification and warrant utter neglect of anatomical evidence. In the first place important generalizations are drawn from the excretion of a few relatively simple substances under certain artificial and pathological conditions. We must confess, however, that very much is still uncertain of the fundamental laws which govern excretion particularly of more complex compounds. We are quite ignorant of the factors, direct or indirect, which may enter into the rapidity and manner of elimination of one or the other substance. It is only necessary to recall here the contradictory results of experimenters regarding the excretion of water and salt in the study of the normal functions of glomeruli and tubules, and the possibilities of compensatory action. We find further a certain variance in these experimental results with the direct anatomical evidence, and herein rests a possibility of error. The anatomical evidence points strongly to the fact that a strict distinction between vascular and tubular

nephritis does not exist, and that the experimental results may be explained by different reasoning. In disease the conditions may be even more complicated. Erich Meyer's[16] observations have led him to similar conclusions. Aschoff[17] and Suzuki's[18] recent experiments have demonstrated with clearness that the effects of poisons on parenchyma cells show important qualitative differences; some, like uranium and mercuric bichlorid, produce necrosis associated at times with a hyaline dropsical degeneration; others, as in the case of cantharidin, with swelling and vacuolization. More particularly in regard to cantharidin, Aschoff found contrary to the generally accepted view tubular lesions and uninvolvement of glomeruli. Aschoff, therefore, concludes that the poisons employed by Schlayer and Hedinger show individual differences and complexity in their topographical action, that cantharidin belongs histologically with greater right to the so-called tubular nephritis and that a division of poisons into vascular and tubular varieties does not seem justifiable. He states: All poisons act primarily on the parenchyma, that is, the different parts of the convoluted tubules; the resulting functional changes are the results partly of the topographical variations in the action of a poison and partly the effects of the poison on blood-pressure. Aschoff's results fully corroborate then the view previously expressed,[19] and emphasizes the necessity of a revision of prevalent ideas regarding the specific actions of poisons. There are other important points in this connection which Aschoff and Suzuki have attacked, notably the significance of vital staining and an attempt to analyze further the structural and functional differences in the tubules. So much remains to be done in this regard that we are far from the possibility of a functional classification of kidney diseases. These considerations do not detract in the least from the value of the experimental observations recorded. They remain important contributions to the secretion of the kidney under abnormal conditions. But one should hesitate, at least at present, to accept these results as a sufficient basis for a classification of kidney inflammations.

But we are even more at a loss in an attempt at clinical classification, which introduces additional difficulties. These have been fully discussed by Fr. Müller, so that it is unnecessary to enter into them again. He pointed out the uncertainty of what is meant by acute and chronic lesions, parenchymatous and interstitial, and the difficulty of the corre-

16. Meyer Erich: Discussion of Schlayer's paper. Kongress für innere Medizin, 27 Kongress, 1910.

17. Aschoff: Zur Morphologie der Nierensekretion unter physiologischen und pathologischen Bedingungen. Vorhandl. d. deutsche. path. Gesellsch., 1912, xvi.

18. Suzuki: Zur Morphologie der Nierensekretion unter normalen und pathologischen Bedingungen. Jena, 1912.

19. See my monograph on Bright's disease, p. 66 B.

lation of the clinical picture and the anatomical lesion. He recommended abolishing the uncertain anatomical nomenclature, and to employ at the bedside only descriptive clinical terms, for instance, instead chronic parenchymatous nephritis, chronic hydropic or anhydropic kidney disease. In view of what has been presented above, Müller's desire to discard old outgrown terms and to substitute a very general directly controllable descriptive terminology is praiseworthy. However, it cannot be regarded satisfactory to employ a purely clinical terminology which at the best is only a repetition of symptoms and gives no idea of the picture of the disease processes underlying them.

Indeed, the desire to correlate clinical symptoms with anatomical pictures is so strong and necessary for the scientific physician that constantly and justly such attempts are being made. The greatest difficulties are encountered, of course, in connection with prolonged kidney diseases, above all the contracted kidney. This finds its reason not only in the complexity of the disease, but in the ever-changing views of pathologists about the origin and nature of that affection. It is, therefore, worth while to present the question of contracted kidney in some detail, as it affords an excellent illustration of the difficulties of an exact classification. The latest most generally accepted views on the pathogenesis and histogenesis of contracted kidney are those of Jores and Prym.

Jores'[20] ideas are to some extent a revival of those of Gull and Sutton, namely, that one type of contracted kidney is arteriosclerotic and not inflammatory. Before Jores, Senator and Ziegler had recognized the direct relationship of arterial changes to contracted kidney and had described a type as arteriosclerotic interstitial nephritis and arteriosclerotic atrophy of the kidney. Jores makes the following subdivisions:

1. The red granular kidney with uniform fine granulations and of brownish-red color, characterized histologically by interstitial growth with atrophic tubules, which show a more or less regular arrangement. Diseased parts interchange with preserved or even hypertrophied parenchyma. Parenchymatous changes are quite inconspicuous or absent, but arteriosclerosis (?) of the small kidney arteries is very marked.

2. The secondary contracted kidney, pale or yellowish pale, characterized histologically by an irregular arrangement of atrophied parts. The still preserved glomeruli present the picture of glomerulo-nephritis. The parenchymatous degeneration is always more or less accentuated, but arteriosclerosis of the smaller arteries is very limited or absent. In this form exists little or no heart hypertrophy; it is marked in Form 1.

20. Jores: Ueber Arteriosklerose der Kleinen Organarterien und ihre Beziehung zur Nephritis. Virchows Arch. f. path. anat. Vol. clxxviii; Ueber die Beziehungen der Schrumpfniere zur Herzhypertrophie. Deutsche. Archiv. f. Klin. Med., 94.

As a result of his largely clinical observations, Volhard[21] has added a third and combined form consisting of 1 plus a nephritis. In Form 1 he found no functional disturbance; in Form 2 a prolongation of water excretion with no power of concentration, and in 3 the same deficiency plus heart hypertrophy. A fourth type of contracted kidney was occasionally met by him without any rise in blood-pressure and functionally related to the secondary contracted kidney (very rare).

Jores' observations have been supplemented by those of Fahr,[22] Gaskell,[23] and lately by an interesting study of Herxheimer,[24] which agrees in the main points with what I have had occasion to observe in this matter. He found even in the early stages of this disease never an entirely healthy parenchyma, although the vascular changes were much more prominent than those in the parenchyma. Nevertheless, I am of the opinion that these parenchymatous changes must be regarded as of some importance in relation to the character of the disease. They are present at a time when nutritive interference by vascular obstruction is out of question and must therefore be attributed to other irritating influences. The characteristic change in the small vessels should not be confounded with the ordinary arteriosclerotic elastic hyperplasia of larger vessels. It consists of a hyaline swelling of the intima associated with the appearance of fatty substances.

According to Herxheimer, it affects frequently the vasa vasorum of larger arteries, but also the vasa afferentia and loops of the glomeruli; he did not observe this in genuine nephritis. Contrary to the findings of Jores, Herxheimer missed this change in other organs with the exception of the spleen. But the latter is of no significance on account of the frequent occurrence of similar vascular changes under all sorts of conditions. Herxheimer regards the vessel lesions as part of general arteriosclerosis, and believes that toxic agents injure the small kidney vessels, thus leading to hypertonia and contracted kidney. He leaves the genesis of the lesion uncertain; it may be due to a direct poisonous action or possibly an indirect result of alterations in kidney tissue or due to nephrotoxins.

Attention has been drawn to similar vascular changes in other organs; for instance, in the capillaries of the islands of Langerhans in the pancreas. It is considered not unlikely that they form a basis for the development of disease in various organs.

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21. Volhard: Ueber die funktionelle Unterscheidung der Schrumpfniere. Kongress für innere Medizin 27. Kongress, 1910, p. 735.

22. Fahr: Ueber chronische Nephritis und ihre Beziehung zur Arteriosklerose. Virchows Arch. f. path. Anat., Vol. 195; Zur pathologisch anatomischen Unterscheidung der Schrumpfniere, etc. Frankfurter Ztschr. f. Path., ix.

23. Gaskell: On the Changes in Glomeruli and Arteries in Inflammatory and Arteriosclerotic Kidneys. Jour. Path. and Bacteriol., 1911, xii, 287.

24. Herxheimer: Verhandl. d. deutsche. path. Gesellsch., 1912, p. 211.

Now, while many modern pathologists are inclined to separate the red granular or so-called primary contracted kidney entirely from the groups of nephritis, it may in my opinion still be questioned whether we are fully justified in doing so, or whether the older standpoint, which included it among the interstitial or productive group of nephritis, has not considerable justification. Mention has already been made of the existence of parenchymatous changes, which, although quantitatively slight, show an injury beyond the vascular districts at a time when they cannot be explained by simple quantitative interference with the nutrition of these parts as a result of the vascular involvement. Furthermore, even with due consideration to the different structure in large and small vessel, the different nature of these vascular changes from arteriosclerotic or atherosclerotic lesions and its uncertain relation to the other arteriosclerotic processes, which Herxheimer himself emphasizes, rather point to a direct toxic effect.

Finally, the early focal accumulation of cells in the immediate neighborhood of injured parts closely resembling certain inflammatory reactions, the subsequent irregular formation of granulation tissue and growth of connective tissue, raise the possibility of more diffuse and specific sclerogenic irritating influences.

Conditions in the kidney may in this regard perhaps be compared to certain affections in the liver, notably the cirrhoses and subacute liver atrophies. Curiously enough, Jores himself has drawn attention to this in connection with a case of subacute liver atrophy presented to the German Pathological Society. Jores[25] says:

"If one goes so far as to regard the destruction of liver tissue as the only essential process and the connective tissue growth only dependent upon this loss, observations which I have made in connection with the case under discussion speak decidedly against such an assumption. For it is noteworthy that in this case of marked destruction of liver parenchyma with a duration of three months, no connective tissue proliferation of consequence has occurred. It demonstrates that besides the loss of parenchyma an additional factor enters into the pathogenesis of liver cirrhosis; this causes the chronic proliferating inflammation, or, as S. v. Heukelom expressed it, an equally effective degenerative and sclerogenic injury of cells." At the same time Albrecht[26] declared that "if one compared these observations (Jores case) with those of ?altauf, who had seen early connective tissue growth in the liver of phosphorus poisoning, one must arrive at the conclusion that in the first instance existed a toxic action on the liver cells alone, while in the second an irritative action on the connective tissue is added. One must question therefore decidedly whether the connective tissue formation in cirrhosis is only the expression of simple scar formation."

It appears that the conditions in contracted kidney are very similar, and indeed, as shown above, interstitial cell foci and thickening occur before loss of parenchyma would call for cicatrization.

25. Jores: Zur Kenntniss der subakuten Leberatrophie. Verhandl. d. deutsche. path. Gesellsch., 1907, xi, 320.

26. Albrecht: In the discussion of Jores article. See note 25.

My experience is that the vascular changes do not even generally assume marked dimensions without simultaneous extension of cellular foci and connective tissue thickening, which seems to indicate that all of these changes are correlated rather than dependent. (Compare the two excellent illustrations accompanying Herxheimer's article in the *Verhandlungen der Deutschen Pathologischen Gesellschaft,* 1912, especially Figure 2.)

It must also be remembered that even extensive arteriosclerosis of small vessels in other organs does not appear to lead to the quantitative and qualitative changes which are characteristic of this form of contracted kidney.

These considerations make it probable that the processes leading to the primary or red contracted kidney are evidences of irritative influences within the kidney, of which the vascular changes only form an early and conspicuous feature.

It is somewhat doubtful whether the three cases which Gaskell reports as representatives of early and more advanced vascular contracted kidney really belong to this category or not, more properly to the arteriosclerotic kidney as recognized by Senator, Ziegler and others. In Case 34 a specific (syphilitic?) etiology may have been involved. It concerned a young man of 34 years, who died with the diagnosis of dementia praecox (?). On autopsy were found focal brain softening due to extensive and pronounced arterial changes (syphilitic?), extending from the basal arteries throughout the brain. History and other clinical data were unsatisfactory; there were no records of blood-pressure or other diagnostic measures. Moderate heart hypertrophy was present. The kidney appeared macroscopically and microscopically normal, except for thickening and fatty changes of arteries and occasional hyaline glomerules. Parenchyma and interstitial tissue were quite uninvolved. The other two cases are even more doubtful in this respect. Case 38 appears typical of the infarcted kidney of arteriosclerosis (Ziegler), and, furthermore, was complicated by a left-sided hydronephrosis and atrophy due to stone. In Case 39 the kidney is described only as decreased in size and the cortex as diminished; no microscopic examination is given.

Frey has also been unable to uphold entirely Volhard's and Jores' contentions, and Krehl[27] is very sceptical in this regard.

Volhard believes that Jores' secondary contracted kidney (macroscopically yellowish, pale, microscopically with accentuated parenchymatous degeneration and typical inflammatory glomeruli, without, or at least with very limited, arteriosclerosis and no heart hypertrophy) occurs even more frequently than the combined form. (Type 3.) Frey, how-

27. Krehl: See discussion of Schlayer's and Volhard's papers. Kongress für innere Medizin., 27. Kongress, 1910.

ever, has not one case in his series of observations which conforms with all the requirements for Type 2 of Jores. In one case existed a blood-pressure of 195; autopsy showed a kidney macroscopically corresponding to this form, and there was little arteriosclerosis, but, contrary to Jores, marked hypertrophy of the heart. Even Roth,[28] who investigated the relationship of arteriosclerosis to contracted kidney in Jores' laboratory, speaks of contracted kidney without arteriosclerosis as an exception, and of the six cases which he reports, three showed some vascular changes. My records agree with Frey's[29] conclusions in so far as occurrence of diseased renal vessels[30] and heart hypertrophy in contracted kidney are concerned. I must believe that both are the rule and that their absence is irregular and dependent on certain other influences: nutrition, atrophy of muscle, edema, rapidity with which the disease leads to fatal issue, etc. There also seems to be no question that the degree of kidney contraction stands in no direct relation to the degree of heart hypertrophy.

Frey[29] is able to recognize a type of arteriosclerotic kidney already acknowledged by Romberg. This form is characterized clinically by stasis. It was formerly regarded as nephritis and is probably identical with what Bollinger and his school described erroneously as *Stauungschrumpfniere*. A previous communication[31] has discussed that feature of the question fully.

In Frey's opinion the old secondary contracted kidney and Jores' Form 2 are practically identical.

According to these modified views, he differentiates between:

1. Vascular contracted kidney (Nephropathia chronica degenerativa sive circulatoria of Aschoff), (a) of larger type (Ziegler's arteriosclerotic kidney); (b) of smaller kidney vessels (may include the red granular type of Jores, and the old primary interstitial nephritis of Senator. It is in my opinion doubtful whether this really corresponds to the primary contracted kidney or interstitial nephritis, both of which are more correctly grouped, as explained above, under the productive nephritis).

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28. Roth: Ueber Schrumpfniere ohne Arteriosklerose. Virchows Arch. f. path. Anat., clxxx.

29. Frey: Zur Pathologie der chronischen Nephritiden. Deutsche. Archiv. f. klin. Med., 1912, cvi.

30. It is questionable whether some of these vascular changes in contracted kidney are not the result of the local inflammatory conditions. A periarteritis may involve the adventitia and perivascular infiltration may combine with fibroblastic proliferation and lead to thickening of the adventitia. This lesion may even extend toward the lumen of the vessel, thereby adding an endarteritis obliterans. A direct toxic action on the intima, particularly in the smaller vessels, appears also very possible. The arterial changes in nephritis need reinvestigation. It appears that some of them do not belong to what is generally grouped as arteriosclerosis.

31. Oertel: The Cyanotic Induration of the Kidney. Jour. Med. Research. Boston, June, 1912, xxvi, No. 2.

2. Parenchymatous contracted kidney (Nephropathia chronica inflammatory of Aschoff) including the old secondary contracted kidney and Jores' Form 2.

3. The combined form of Volhard: nephritis plus arteriosclerosis.

According to Frey, these types differ correspondingly clinically thus:

Form 1, with high blood-pressure and urine stasis (the exact type, a or b, cannot be diagnosticated).

Form 2, with dilute urine, inability of the kidney to concentrate, no heart hypertrophy or high blood-pressure.

Form 3, like 2 but plus high blood-pressure and heart hypertrophy.

There are, of course, exceptions; the vascular type may show no urine changes, provided the heart action is good; specific gravity and power of concentration may then be normal. Again, the parenchymatous forms do not necessarily show typical functional disturbances.

Volhard's views may be summarized in this regard thus:

Form 1, normal concentration and water excretion, normal excretion of NaCl and nitrogen.

Form 2, hyposthenuria, compensated by polyuria (see Schlayer's explanation above) as long as there exists relative sufficiency of the kidney.

Form 3, combination form, probably dependent on a predisposition of Form 1 to acquire nephritis. In Volhard's opinion, it is the old genuine contracted kidney, and has a tendency to uremia.

Anatomical as well as clinical subdivisions of contracted kidney are, therefore, still much under discussion, and their character uncertain, particularly whether the old primary or genuinely contracted kidney is only arteriosclerotic in character, or whether it represents, as I am inclined to think, an inflammatory lesion with characteristic involvement of small vessels, or whether, finally, a combination of arteriosclerotic changes superseded by nephritis as Volhard believes.

In view of the complexity of the matter and the number of divergent and constantly changing views about the nature of these processes does it appear possible to arrive at any classification at all?

Indeed Krehl's remarks at the Congress for Internal Medicine in Wiesbaden in 1910 were very sceptical.

I shall endeavor in the second part of this paper to show just how far a classification appears possible.

II.

CLASSIFICATION

It must be emphasized that all classifications in medicine as well as in other branches of science carry with necessity the weakness inherent to the greater or lesser artificiality of all scientific definitions. Theseus, we are told, erected on the Isthmus of Corinth a column bearing on one

side the inscription, "Here is the Peloponnesus and not Attica," and on the other, "Here is Attica and not the Peloponnesus." But no scientific investigator could safely imitate this mythic hero, for the complexity and variability of all natural phenomena make similar strict divisions based on individual observations and ideas easily vulnerable and perishable. The scientific investigator must remain conscious of the fact that his classifications are working tools for the study of phenomena, which in reality lack isolation, but are actual only in their genetic relation and interdependence with others. Processes defy strict classification; only the fossillized remnant may be embalmed and laid at rest in a final system.

A classification, therefore, in order to be applicable to processes of life, may only cover general characteristics. It must confine itself to the substance, the nucleus of the matter, for as soon as it extends to the side lines it merges imperceptibly with others which confuse and defeat the very purpose for which it was designed.

Thus an exact classification which, not unlike that of an *actio finium regundorum* in Roman law, attempts to draw sharp boundary lines between it and its neighbors, attempts a separation, which in reality does not exist, and which in practice leads to serious disadvantage and away from truth.

Mention should perhaps here be made of a psychological complication in attempts at classification. They naturally reflect the view-point of the observer. Whatever appears most readily in the classifier's field of vision, or that which he is in the habit of thinking in, is to him the most important principle. It colors his whole scheme. It is difficult, for instance, for a morphologist to think in other than visual conceptions; his ideas represent definitely related morphological processes; one trained only in physiological methods of research needs much less a dominant morphological substratum for a satisfactory conception.

Now if one studies carefully the complicated situation which has been outlined above, one must, I believe, come to the conclusion that it is unsafe, at least at present, to leave entirely the ground of objective morphological experience. For etiological, histogenetic, functional and clinical facts at our disposal are, in the first place insufficient; in the second place too variable to serve as basis for a classification of nephritis. It appears equally mistaken, however, to introduce subjective views regarding the character of anatomical processes, or to separate more or less arbitrarily certain parts which experience has shown in close union with others. Nothing, it appears, is gained by such procedure; it is a source of confusion, leads to academic discussions and does not aid in the understanding of the nature of a disease at all. Marchand properly questions what would be gained by speaking of an inflammatory neph-

rosis, instead of an inflammation or of a degenerative or parenchymatous nephrosis? Shortly before his death, Senator expressed to me similar views. Indeed, such individual opinions and ideas regarding the nature of pathological processes change so frequently and there exist so many at one time that one can find, for instance, in a modern text-book of pathology, written by leading pathologists, three different ideas and descriptions of the inflammatory process. And that particular book is for students and practitioners.

Observation shows that "inflammation" is composed of a number of processes, which, on account of their close genetic relation and interdependence and more or less definite course, may be conveniently regarded as a unit. In other words, it is the sum total of processes which appear as the result of certain irritations. But if we go beyond this and assume on the basis of theoretical considerations which can be neither entirely proved nor disproved, that the nature of inflammation is only degenerative, or that it is only reactive for purposes of defense, and that the term inflammation should be restricted to one or the other of these features, then we introduce arbitrary lines of demarkation based on personal opinions and build on these unstable systems. This situation is not improved by the fact that another difficulty arises immediately in determining what is to be included under the passive and what under the reactive phenomena. Some, for instance, regard parenchymatous degeneration as a passive process; others as an active response to an inflammatory stimulus.

Thus the present discussions about the nature of inflammation resemble somewhat the discussions of the old psychologists about the nature of the soul. They gave first a metaphysical definition of the soul, then arranged facts according to it. A greater uniformity of views and a more satisfactory classification in psychology were only reached after psychic phenomena were no more regarded as isolated units or transcendental forces, and after it was appreciated that "soul" is a convenient term for the sum total of our inner experience. Medicine in general still suffers more than other sciences from an effort at medieval definitions. These, however, are for reasons previously given, impossible.

I attempted, therefore, several years ago[32] to rehabilitate a purely descriptive anatomical classification which has the advantage of compatability with the needs of the clinician and pathologist. It assumes that nephritis designates a unit from beginning to end, and therefore includes all processes which may enter into or may directly modify the expressions of this inflammatory process. It touches in no way on the disputable pathogenesis or the varying topographical involvement, both of which go beyond the possibility of a general classification. It indicates only the predominating pathological feature or features.

32. Oertel: Bright's Disease, pp. 22-26, 214-215.

The idea of a descriptive anatomical principle for classification is not new. It was successfully, if only partly, followed by Cohnheim, Orth and others and in this country by Delafield. They used the terms degenerative, exudative, productive or proliferative as useful qualifying adjectives. But following Müller's suggestions and efforts to eliminate antiquated and misleading terms entirely, I propose to go further and make it the underlying foundation for the entire system of classification of the inflammations of the kidney.

Such a classification may be held to be too broad, and therefore insufficient, but it may be properly questioned for reasons previously discussed, whether a scientific classification may offer more than an expression of fundamental or general characteristics.

We obtain thus a classification by groups rather than by individual diseases, and it is my belief that with growing knowledge and necessarily growing differences of opinion in regard to the exact place of diseases, classification by groups will become the best means to serve the more general needs of the physician without interfering with the necessary freedom of thought and opinion of the scientific investigator.

We may, accordingly, draw the following sketches:

1. The group of *simple nephritis,* in which occurs cloudy swelling and parenchymatous degeneration, inflammatory edema and serous exudate, associated at times by desquamation and inflammatory proliferation of parenchyma cells. Restitution to integrity.

2. The group of *degenerative and exudative nephritis,* destructive in character; represented by marked and extensive degeneration and necrosis of parenchyma cells, cellular exudate, occasionally, with hemorrhages into glomeruli, periglomerular and intertubular tissue and into tubules. Proliferation of parenchyma cells in glomeruli and tubules, abundant cast formation. The predominating feature may exist either on the degenerative or exudative side.

3. The group of *degenerative and productive nephritis,* destructive and constructive in character; with prominent degenerative, largely fatty changes, much slighter and frequently more localized exudative processes, proliferation of parenchyma cells with the formation of epithelial giant cells, cast formation, appearance of leukocytoid and fibroblastic cells, loss and collapse of glomeruli and tubules, gradual formation of mature fibrous tissue overgrowing wasted and wasting parts, first patchy, then more diffuse. Occasional hemorrhages. Thickening of renal arteries, occasional formation of infarcts.

4. The group of *productive nephritis,* associated with a marked reconstruction of kidney cells and architecture.

a. Diffuse: With less violent but general degeneration and loss of parenchyma and glomeruli by inflammatory obliteration. Marked

regeneration of flat and syncytial-like tubular epithelium with marked distortion of the tubules, and associated abundant irregular overgrowth of connective tissue. Arteriosclerosis of kidney arteries usually prominent; infarct formation occasional (includes in general the old secondary contracted kidney and Jores Form 2, Frey's Form 2, Volhard's Form 2 and probably cases of Form 3. Nephropathia chronica inflammatoria of Aschoff).

b. Focal and patchy: Characterized early by a hyaline swelling and fatty degeneration of intima and endothelial cells of the small renal vessels and capillaries, associated with cellular interstitial and periglomerular cell foci and focal parenchymatous degeneration. All of these acquire gradually more momentum, but the involvement of the small vessels remains most conspicuous. It leads to obliteration of their lumen, thereby adding quantitative to the qualitative disturbance. Thus results collapse of affected parts, the extent of which necessarily varies, so that at times the superficial appearance of the kidney may be only very finely granular. The extent of new connective tissue formation is also correspondingly irregular, usually most pronounced around Bowman's capsule. The tubules are relatively well preserved until late in the disease, and epithelial desquamation is insignificant. The disease is usually accompanied by arteriosclerosis of the kidney arteries. (Includes in general, Jores' Type 1, Frey's Type 1, Subdivision b, and Volhard's Type 1, and possibly cases of Type 3. Nephropathia chronica degenerative sive circulatoria of Aschoff. The old genuine contracted red kidney or primary interstitial nephritis.)

The difference between a and b lies in the fact that in a, a relatively strong or decliningly strong irritative influence has affected the kidney very diffusely, perhaps as the result of a previous severe degenerative and exudative nephritis; in b, a much less severe but persistent irritant, which is never sufficiently strong to produce severe diffuse degeneration and exudation, gradually involves the kidney in disease. It naturally affects the walls of the smaller blood-vessels and the glomeruli prominently first, on account of their exposure by virtue of anatomical structure to irritants and blood-pressure. By almost simultaneous extension of its irritating influence it attacks patches of parenchyma and the neighboring periglomerular parts which respond by focal cell accumulation. Their appearance is then manifest, as we have seen, before any quantitative interference by vascular obliteration is possible. In all forms of contracted kidney heart hypertrophy is the rule.

Finally, one may group as independent non-inflammatory affections the senile atrophy and the true arteriosclerotic atrophy of the Ziegler type. The latter is plainly characterized by patchy loss of substance due to elastic thickening and gradual obliteration of arteries alone. It does

not show an atrophy of glomeruli or tubules due to other reasons; scar formation remains, therefore, quite limited and follows strictly in the path of the lost substance.

In a previous communication,[33] it has been shown that a cyanotic induration, *Stauungschrumpfniere,* does not exist, and that cases thus described are either of Groups b, productive nephritis, or of the arterio-sclerotic non-inflammatory atrophy of the kidney associated with stasis.

30 West Forty-Fourth Street.

33. Oertel: The Cyanotic Induration of the Kidney. Jour. Med. Research, Boston, 1912, xxv, No. 2.

THE ETIOLOGY AND TREATMENT OF HEMOGLOBINURIC FEVER

A REPORT OF FIVE HUNDRED AND FOURTEEN CASES *

CARL LOVELACE, M.D.
WACO, TEXAS

The exact etiology of hemoglobinuric fever is still undetermined. It has been considered the result of pernicious malarial infection in instances in which quinin will give relief;[1] others consider it evidence of quinin intoxication;[2] still others that we have here a duplex disease,[3] quinin in some cases giving relief, in others hastening a fatal termination, a disease *sui generis*,[4] where quinin is neither injurious nor beneficial. Some have advised the use of quinin only when the parasites can be demonstrated in the peripheral blood,[5] still others believe that hemoglobinuric fever can be avoided if the quinin is given intramuscularly.[6]

Considering, then, the conflicting opinions as to the nature and treatment of hemoglobinuric fever, it is hoped that this article, based on 514 cases of blackwater fever, treated by American physicians in the hospital of the Madeira-Mamore Railway Company, Porto Velho, Brazil, between Jan. 1, 1908, and Nov. 27, 1912, may be of interest.

It is proposed to consider: (1) the relation of the disease or condition to malaria; (2) its relation to a particular species of malarial parasite; (3) its relation to quinin; (4) its racial and personal incidence.

Under treatment, it has seemed best to discuss: (1) the results of treatment with quinin; (2) the results of treatment without quinin; (3) the general treatment of the condition, and (4) the relation of the quinin prophylaxis of malaria to blackwater fever.

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1. Brem, Walter V.: Malarial Hemoglobinuria. Jour. Am. Med. Assn., 1906, xlvii, 1896.

2. The Quinin Theory of Blackwater Fever, suggested by Vertas, a Greek physician, in 1858; supported by Koch, Plehn, Tomaselli and others. Manson, Sir Patrick: Tropical Diseases, p. 238.

3. Brem, Walter V.: Studies of Malaria in Panama, II. THE ARCHIVES INT. MED., 1911, vii, 153.

4. Manson's Theory; supported by Craig, C. F. Is Hemoglobinuric Fever a Manifestation of Malaria or a Disease Sui Generis? THE ARCHIVES INT. MED., 1911, vii, 56.

5. Bastianelli's rule quoted universally. Manson: Tropical Diseases, p. 244.

6. Castellani and Chalmers: Manual of Tropical Diseases, p. 696.

RELATION TO MALARIA

(1) Of 327 cases of blackwater fever treated in this hospital between Jan. 1, 1911, and Nov. 27, 1912, malarial parasites were found in the peripheral blood in 145, or 44 per cent., either on admission or within a few days thereafter. This becomes more significant when the following circumstances are considered: (a) In a majority of the cases only one blood examination was made, and it was made during the period of hemoglobinuria. (b) Over a considerable portion of the period of time here considered it was my custom to begin quinin very shortly after the disappearance of the hemoglobinuria, so that subsequent examinations were almost necessarily negative. During the year 1912, when the interim between the termination of the hemoglobinuria and the resumption of quinin was longer (five to seven or more days), blood examinations were made more frequently, with the result that the blood-slides of seventy-nine out of 153 cases of blackwater fever showed malarial parasites, a percentage of 51.5. (c) In the considerable number of cases in which quinin has been deliberately withheld for the purpose of making blood examinations, parasites have appeared within fourteen days in all instances save one. At least ten such experiments were made within the year 1912.

(2) No case of blackwater fever has been observed in which there was not a history of a fever, apparently malarial, a few days or weeks previously. Almost invariably there is the history of many attacks extending over many months.

(3) In no instance has hemoglobinuria been observed as a concomitant of a first attack of malaria.

Sick men, not well men, are the ones who have blackwater fever. Men who have lived here some months, who are anemic, whose spleens are enlarged, who are in the habit of having fever every few days or weeks, who, as a rule, take quinin irregularly and inadequately, who insist on getting up and about their businesses immediately after a malarial paroxysm—these are the men whom one soon learns to classify as "blackwater candidates."

BLACKWATER FEVER AND THE TERTIAN PARASITE

J. W. W. Stephens has attempted to account for the absence of blackwater fever in Ceylon by the rarity of the estivo-autumnal parasite there.[9] Deaderick writes that "only exceptionally is hemoglobinuria associated with the benign organisms."[10] Christophers and Bentley, in explaining the hemolysis, assume that the estivo-autumnal parasite is the primary

9. Castellani and Chalmers: Manual of Tropical Diseases, p. 691.
10. Deaderick, W. H.: A Practical Study of Malaria, p. 153, *et seq.*

cause of the condition.[11] Brem states that, in Panama, the estivo-autumnal parasite is nearly always the one concerned.[12]

There is a general tendency to regard the association of the tertian parasite with blackwater fever as accidental; and to assume that the estivo-autumnal parasite must also be present, although perhaps not demonstrable in the peripheral circulation.[13]

It is believed that the accompanying tables present evidence for regarding the tertian parasite as a factor, at least as important as the estivo-autumnal, in the production of blackwater fever. Table A is a record of the blood examinations in the Candelaria hospital during the past twenty-sixth months. It shows, simply, that the estivo-autumnal

TABLE I.—Record of Blood Examinations for Malaria in the Candelaria Hospital, from September to October, 1912, Inclusive

Period	Total Blood Examinations	E.-A.	Tertian	Quartan	E.-A. and Tertian
Sept. to December (inclusive), 1910	2257	831	359	..	63
Year 1911	8029	3130	1481	6	181
January to October (inclusive), 1912	6148	2027	920	10	147
Totals	16434	5988	2760	16	391

TABLE 2.—Blood Examinations of Blackwater Fever Patients in the Candelaria Hospital, 1910, 1911 and 1912

Period	E.-A.	Tertian	E.-A. and Tertian	Negative	No Report
1910—(deaths)	1	1	0	4	5
(discharges)	19	22	1	31	51
1911—(deaths)	3	4	0	8	0
(discharges)	24	23	1	88	2
1912—Jan. to Oct., inc. (deaths)	3	4	0	12	0
(discharges)	37	20	15	62	..
Totals	87	74	17	205	58

parasite occurs here with more than twice the frequency of the tertian parasite. Table B is a record of blood examinations in the blackwater fever patients during the same period. It is seen that, while the total occurrence of the estivo-autumnal parasite is twice that of the tertian, its occurrence in patients ill of blackwater fever is only slightly greater than that of the tertian parasite; that is to say, a man in this region who harbors the tertian parasite, has nearly twice the liability to hemoglobinuria of a man who harbors the estivo-autumnal parasite. These blood-examinations have been checked, at intervals, over considerable

11. Castellani and Chalmers: Manual of Tropical Diseases, p. 692.

12. Brem, Walter V.: The Etiology of the Erythrolytic Type of Hemoglobinuric Fever. The Archives Int. Med., 1912, ix, 129.

13. Deeks, W. E. and James, W. M.: Pacific Med. Jour. 1912, lv, 347.

periods of time, by Dr. J. S. Forsythe, Dr. E. J. Whitaker and Dr. A. M. Wolcott. During the past eighteen months particular attention has been paid to identification of the species of parasite in cases of hemoglobinuria.

It is believed that, assuming the malarial origin of the condition, the number of cases is sufficient to justify the assertion that the tertian parasite cannot, in this region, be excluded as an important factor in blackwater fever. In this connection it may be well to state that, while the tertian parasite is apparently not concerned in any of our cases of "pernicious malaria," it is here an extremely persistent infection. More time and more quinin are required for its eradication than for that of the estivo-autumnal parasite. In saying this, I am not unmindful of the fact that I have seen crescents persist in the peripheral circulation after quinin, in full doses (30 to 40 grains), had been given daily for three weeks. Every physician here who has correlated his clinical and his laboratory work has been struck by the rapid blood destruction in, the great prostration incident to, and the diabolical persistence of tertian infections. I cannot here enter into the proof of these unorthodox statements. I set them down because I believe them to be true and because of their bearing on a question which has not had the consideration that it deserves, viz., that of the local variations of malaria. One cannot read the treatment of malaria as set forth in many of our text books without being struck by the mildness of the measures considered adequate to cure it.

BLACKWATER FEVER AND QUININ

The association of quinin in this series of cases of blackwater fever has, I believe, been invariable. Always there is the history of quinin in one or more small or large doses having been taken a few hours before the onset of the characteristic symptoms. Once these symptoms have occurred, however, they are prone to recur while the patient is still in bed, even without quinin or without any other apparent extrinsic cause. At times these recurrences are coincident with the demonstrable sporulation of a group of malarial parasites. More frequently the blood is negative. In one of Whitaker's cases, there were six such recurrences spread irregularly over three weeks.

Recurrences after the patient is up and about — that is, *repeated attacks* — seem, here, to be brought about in the same manner as the first attack; they follow a dose of quinin taken for what appears to be a frank demonstration of malarial infection. One of our employees treated successively by the writer, Forsythe, Wolcott, Nutter and Whitaker, had fourteen such attacks in three years. In each instance a dose of quinin was followed by one or more paroxysms of hemoglobinuria, which paroxysms were in turn followed by a temporary cessation of the active symptoms of malarial infection.

In an intensely malarial region it is of course quite natural that a man should, when he begins to feel ill, forthwith take a dose of quinin. Nevertheless, we do receive a goodly number of simply malarial patients who have not taken quinin; we do not receive any blackwater patients who have not taken quinin shortly before the appearance of the hemoglobinuria. It is by no means an uncommon spectacle to see a malarial subject develop blackwater fever in the hospital after the administration of quinin. For the past three years I have used the hydrochlorid of quinin almost exclusively, except for intra-muscular injections. To see the urine of a malarial patient become hemoglobinous after the administration of quinin hydrochlorid has been, in this hospital, an event too common for more than a passing comment.

RACIAL AND PERSONAL INCIDENCE

The well-known relative immunity of the negro and negroid races to blackwater fever is very well shown by our records. Of 26,656 admissions for all causes in the past forty-six months, there were 4,537 West Indian patients. These contributed only five to 493 cases of blackwater fever. Two of these were full-blooded negroes. Among 5,751 Brazilian admissions, there were fifty-two cases of blackwater fever. The white Brazilians and, to a lesser degree, those of mixed white and Indian blood, are the ones in whom the disease occurs. The possession of negro blood seems to confer an almost absolute immunity. The possession of aboriginal Indian blood confers only a certain degree of immunity.

During the same period among 6,121 admissions to our Spanish ward, there were 245 cases of blackwater fever; that is to say, 23 per cent. of the total admissions, for all causes, furnished 50 per cent. of the blackwater fever patients.

Among 14,759 European and white North American admissions, there were 390 cases of blackwater fever. The Spaniards forming 41 per cent. of the white admissions, yielded 60 per cent. of the blackwater fever. In other words, the liability of the Spaniard to blackwater fever is, here, twice that of other white men. It is more than 50 per cent. greater than that of the Portugese. It is, of course, absurd to consider the remarkably high incidence of the condition among the Spaniards as due to any special racial susceptibility. The explanation lies in the character and habits of the Spanish laborer. Where another man would be glad to go to the hospital, the Galician peasant, when he is working by contract, will dose himself with quinin and continue to work. He will not sleep under a mosquito net and is, therefore, being constantly reinfected with malaria. He takes a great deal of quinin irregularly. He is, more than any of his fellow laborers, a half-treated subject of chronic malaria.

Our Greek laborers, who take 10 grains of quinin daily with clock-like regularity, are relatively free from malaria and, therefore, from hemo-

globinuria. This I think, is not due to any racial immunity, but to their character and habits; that is, their obedience to instructions in the matters of mosquito protection and quinin prophylaxis. The liability of the Greek to blackwater fever in his own country is notorious.

The transient character of a population of railroad employees in the tropics makes it difficult to present figures which show accurately the manner in which length of residence in this region affects the incidence of blackwater fever. In general, people not previously infected with malaria, do not suffer from hemoglobinuric fever until after eight or ten months here. Individual history with reference to malarial infection and the treatment thereof appears to determine susceptibility. The condition developed in one of my patients ten weeks after his arrival, but he had had a severe attack of malaria two weeks after arriving and recurrent attacks weekly until the onset of the hemoglobinuria.

One may say, then, that here the negroids have an almost absolute immunity to blackwater fever; that the people originating from the aboriginal inhabitants have a considerable relative immunity, and that there is a distinct personal immunity among Europeans and white North Americans, conferred by the prophylaxis and proper treatment of malaria.

THE TREATMENT OF BLACKWATER FEVER

The first question here is the much vexed one of quinin. All discussion is futile save that which presents actual figures for comparison.

During the year 1908, ten cases of blackwater fever were treated here by the method of giving quinin as in ordinary malaria. Of these, three died. During the year 1909, sixty-eight cases were treated here; some with and some without quinin. Of these, seventeen died. Our mortality, up to Dec. 31, 1909, was, then, 25.6 per cent. At this time I felt that it was justifiable to give quinin to a blackwater fever patient. Reports of cases treated in Panama by the quinin method had shortly before been published,[1] and the canons of Bastianelli, pronounced "sensible" by Manson, and quoted, apparently with approval, by Osler, enjoined quinin whenever parasites were found in the patient's blood.

Toward the end of the year 1909 it was decided to treat all cases of blackwater fever without quinin, whether or not parasites were present. Except in two or three regretted instances this decision has been adhered to. Disregarding these, 436 cases have been treated without quinin. Of these, fifty-one have died — a mortality of 11.6 per cent.

J. W. W. Stephens[14] gives the mortality of blackwater fever at from 10 to 20 per cent. Deaderick cites 1,006 patients treated without quinin, with a mortality of 11.1 per cent.; 472 patients treated with quinin, with a mortality of 25.9 per cent., and 3,210 patients treated by both methods

14. Osler's Modern Medicine, i, p. 449.

with a mortality of 21.3 per cent. Considering that nearly all of the patients treated in this hospital were drawn from immigrant railroad laborers, who worked under a tropical sun, lived crowded together in hastily improvised huts and tents, and suffered much from the ravages of beriberi and bacillary dysentery, it is believed that a death rate of 11.6 per cent., under a non-quinin régime, is sufficient reason for questioning the soundness of Bastianelli's oft-quoted rule that quinin should be given to a patient with hemoglobinuria if parasites are present in the peripheral circulation.

But it is not only empirically that this rule is unsound; it is an indisputable fact, as shown by Stephens, that malarial parasites are practically always present in the peripheral blood of blackwater patients in the beginning of, or just before, the attack, and that they disappear from, or become scarce in the peripheral blood very soon after the urine becomes hemoglobinous. Indeed, a paroxysm of hemoglobinuria in a malarial patient may be compared to a single intravenous injection of salvarsan in a syphilitic patient. The parasites disappear more or less from the blood of the former, just as the spirochetes do from the lesions of the latter. If, then, one sees his patient at, say 8 a. m., parasites will be present, and quinin should be given. If he does not see him until noon, the parasites, with their containing cells, will have been destroyed. Therefore, quinin should not be given. The rule is, itself, *prima facie* evidence that its author believed quinin capable, under certain conditions, of inducing hemoglobinuria, yet the administration of the drug is made to depend on whether the physician sees his patient one hour or four hours after the hemoglobinuric condition has developed.

The truth is that this teaching was a groping, tentative half-step in the right direction; in the right direction because it prescribed what not to do in about one-half the cases. In the light of present-day knowledge it is irrational. In the light of the actual recorded experience of physicians the world over it is a dangerous teaching and it should disappear utterly from the text-books of medicine.

The foregoing applies, of course, to the treatment of blackwater fever during the period of hemoglobinuria. When this has cleared up, when hemoglobin casts are no longer to be found and when the icterus has more or less disappeared, the question of treating the malaria — which question was solved temporarily by the destruction of a great many of the parasite-containing corpuscles — will have to be met. (It was met in one of my wards since this paper was written by the intramuscular injection of 7½ grains of quinin. In two hours the hemoglobinuria reappeared and that night the patient died.) Quinin will have to be given, but there need be no hurry about beginning it. If parasites reappear in the blood, they will be scant. Usually their presence will be attended by little or

no constitutional disturbance, even during sporulation, provided the patient be kept at rest. There may be a chill and fever, but, as a rule, the fever, even though the parasites be of the estivo-autumnal type, will be intermittent or markedly remittent. It is not dangerous. The danger lies in the more or less unavoidable resumption of the quinin which precipitated the paroxysm of hemoglobinuria. Neither parasites in the blood, nor chill and fever, with or without parasites, indicate quinin until the urine has been clear for several days. Of course, the blood should be examined daily, in the exceedingly remote event that a heavy infection might reveal itself. It is our practice here to begin with one-grain doses of quinin tannate three times a day and gradually to work up to 20 or 30 grains of the hydrochlorid daily. The tannate is chosen, not because it is a tannate, but because it is the weakest of the salts of quinin.

From the foregoing one may see that I have the following working conception of blackwater fever: It is, as Stephens says, a condition, not a disease; a condition incident to an heroic effort of Nature to rid the organism of the products of long-continued, and, perhaps, "exalted," malarial infection.

GENERAL TREATMENT

The general treatment of the condition is nearly as important as the abstinence from quinin. The chief indications are two: to supply water abundantly and to nurse carefully. On account of the distressing vomiting, it is usually necessary to supply the water as normal saline solution by bowel, by hypodermoclysis, or intravenously, according to the urgency of the case. As a rule, the "Murphy drip," given continuously, at the rate of 75 drops to the minute, is quite satisfactory. The vomiting and hiccough are frequently distressing symptoms difficult to meet. For the vomiting the best treatment is to refrain from putting anything whatever into the stomach and to put a mustard plaster over it. If these fail, it is well to make the patient drink a glass of water, into which two or three drams of bicarbonate of soda are dissolved. After this is vomited more or less relief frequently ensues. Should these simple measures prove unavailing, the changes may have to be rung on the usual remedies and the usual morphin finally resorted to. It is, however, distinctly harmful and we should turn to it only in despair.

Digitalis and caffein, both given intramuscularly and in full doses, are of decided value in the progressive heart weakness, and as promoters of renal activity. Yorkes'[15] studies on the mechanism of the suppression of urine in blackwater fever have shown very clearly the importance of sustaining a relatively high blood-pressure by means of fluids and of these drugs.

15. Yorke, Warrington: Brit. Med. Jour., 1911, ii, 1272.

Careful intelligent nursing that saves every particle of the patient's strength is of immeasurable value. A blackwater patient is emphatically a bed patient. He should be carefully watched not only during the period of hemoglobinuria, but for many days thereafter. Sudden death, by acute cardiac dilatation, during convalescence, as a sequence of getting out of bed, occurred in three of our cases.[16]

QUININ PROPHYLAXIS AND BLACKWATER FEVER

Whoever has read thus far has probably been struck by two things: (1) the remarkably high incidence of, in Deaderick's phrase, the "mystic syndrome" among our employees, and (2) the large size of the prophylactic doses of quinin that we urge on them.

The principle of the prophylaxis of malaria by means of quinin does not, I think, need discussion. Without this measure, the present successful attempt to build the Madeira-Mamore Railroad would have ended in failure, as did the three previous attempts. I have been in the habit of urging all employees, not protected by screened houses, to take 10 grains of quinin daily, for the simple reason that smaller doses have, by actual trial, in the persons of thousands of men, been found to be far less efficient. Unfortunately, our organization is a civil, not a military one. We cannot compel our people to take quinin except when they are in the hospital. We must rely on moral suasion. The result is that some of our employees take 10 grains of quinin daily; a larger number of them take it irregularly, and a not inconsiderable number of them take absolutely no quinin, except when they are sick in bed. Now, we know, by careful observation extending over five years, that among our regular takers of quinin, blackwater fever is exceedingly rare. It does occur among them sometimes, but in these individuals there is always the history of many mild attacks of malaria, extending over many months, in spite of the daily quinin. Of those who take a good deal of quinin irregularly, and among whom the incidence of the condition is very high — 4 per cent. of all admissions for all causes — the Spanish laborer is preeminent. I have already touched on this man's habits. In the first place he will not begin prophylactic doses of quinin until after malarial infection has already revealed itself in the form of a series of blood-destroying paroxysms. This, I may here say, is the serious drawback to the prophylaxis of malaria by means of quinin; it takes a good stiff attack to teach the average man — American foreman as well as Spanish peasant — that, except in our towns where antimosquito work has been done, he must take quinin daily in order to live and work here. After two or thee sporulations have occurred the mischief has been done, and the only way to keep your man from becoming a subject of chronic

16. The many interesting questions connected with post-hemoglobinuric fever are deferred for future consideration.

malaria and, therefore, a candidate for blackwater fever, is to put him in the hospital and give him 30 grains of quinin every day for two or three weeks. To return to our Spaniard: after having had a few attacks of malaria he begins taking quinin irregularly and resumes the pick and shovel. Malarial paroxysms recur every one or two weeks. As he uses the mosquito net, which we have forced on him, as a pillow instead of as a protection against mosquitoes, he is constantly being reinfected. Every attack saps more and more of his vitality. Finally comes the state described by Stephens, that "condition in which quinin, other drugs, cold, or even exertion, may produce a sudden destruction of red cells." In my cases, however, the exciting cause has always been quinin.

Among those of white blood who take quinin only when they are compelled to do so, blackwater fever is common. The condition developed in one of our patients — a Christian Scientist — after a single dose of 5 grains of quinin had been taken. The man had, in camp, two previous definite and separate attacks of chill and fever. On the third attack, at the entreaties of his friends, his religious scruples weakened, and he took 5 grains of quinin. In a few hours hemoglobinuria supervened and the next day he died. This 5-grain capsule of quinin was the only quinin the man had ever taken in his whole life. I do not know absolutely that the two previous definite attacks of chill and fever were malarial, but, if they were not, then this man was the only one of the party of engineers who escaped malaria during that period. No autopsy was held.

Blackwater fever is increasing among our employees. Its incidence is three times as high this year as it was in the year 1909; but in 1909, when a man had had a few attacks of malaria, he usually left the region. This condition of affairs does not now obtain. We are acquiring a population of men who have been here more than one year, men who, by reason of their intensely malarial surroundings and their failure to carry out the quinin prophylaxis properly, have become "blackwater candidates."

SUMMARY

1. There exists a deplorable confusion as to the cause and treatment of blackwater fever.

2. So far as may be indicated by this series of 514 cases, malarial infection stands in a direct causal relation to blackwater fever.

3. Blackwater fever is not due to a particular species of malarial parasite.

4. Quinin, in large or small doses, was, in this series, an invariable antecedent of the hemoglobinuric condition.

5. Under no circumstances[17] should quinin be given to a blackwater fever patient during the period of hemoglobinuria, nor for several days thereafter. The effect of the paroxysm of hemoglobinuria is, itself, that of a drastic, but temporary, therapeutic agent, decimating the malarial parasites in the patient's blood much as a single intravenous injection of salvarsan decimates the spirochetes of syphilis in the lesions of that disease.

6. Quinin, cautiously begun, will be necessary, but it should not be begun until several days after the urine has become free from hemoglobin.

7. Measures which sustain the blood-pressure are urgently indicated during the period of hemoglobinuria. Of these, normal saline solution given by bowel, subcutaneously, or intravenously, is chief. Digitalis and caffein are of decided value.

8. The prophylaxis of malaria is the prophylaxis of blackwater fever.

Candelaria Hospital.

17. Since this paper was written I have read a report of J. B. Cardamatis. Sixty-five physicians report 1,906 cases of blackwater fever treated with quinin, with 255 deaths, a mortality of 23.6 per cent. Forty physicians report 1,066 cases treated without quinin, with 80 deaths, a mortality of only 7.5 per cent. Cardamatis, John P.: Bull. Soc. de path. exotique, 1910, iii, 104.

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